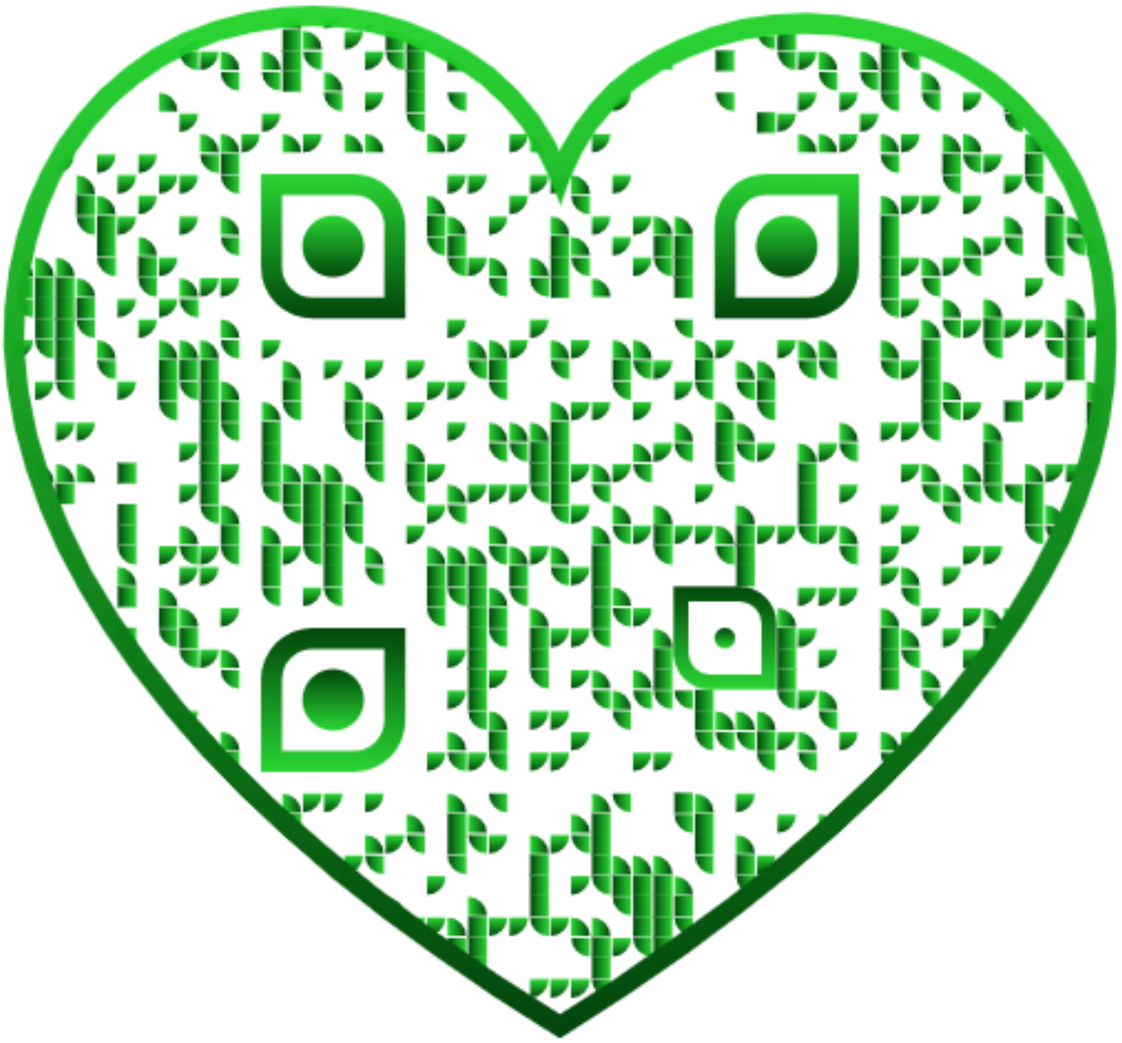
American College of Clinical Pharmacy

Updates in Therapeutics®:
Pharmacotherapy Preparatory Review and Recertification Course

2021 Edition
Volume 2



Senior Director of Professional Development and Member Services: Nancy M. Perrin, M.A., CAE
Associate Director, Professional Development & Marketing: Joanna Gillette
Senior Project Manager: Hannah Keal
Senior Medical Editor: Kimma Sheldon-Old, Ph.D.
Cover Design: Dane Anderson; Layout: Steven M. Brooker

For order information or questions, contact:
American College of Clinical Pharmacy
13000 W. 87th St. Parkway
Lenexa, KS 66215-4530
Telephone: (913) 492-3311
Fax: (913) 492-0088
accp@accp.com
www.accp.com

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Note: The authors and publisher of the Pharmacotherapy Preparatory Review and Recertification Course recognize that the development of this material offers many opportunities for error. Despite our very best efforts, some errors may persist into print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to check other published sources to be certain that recommended dosages and contraindications are in agreement with those listed in this book. This is especially important in new, infrequently used, or highly toxic drugs.

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Errata: When possible, corrections to this publication are included in the 2021 Pharmacotherapy Preparatory Review and Recertification Course Errata, which will be available beginning May 17, 2021, at www.accp.com/media/ppc21/errata.pdf.

Continuing Pharmacy Education:
The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Universal Activity Numbers for the Pharmacotherapy Preparatory Review and Recertification Home Study Course, 2021 edition, are as follows: Pharmacokinetics: A Refresher, Men's and Women's Health, Pediatrics, and Policy, Practice, and Regulatory Issues, Activity No. 0217-0000-21-094-H04-P, 5.0 contact hours; Biostatistics: A Refresher, Study Designs, Chronic Care in Cardiology, and Acute Care in Cardiology, Activity No. 0217-9999-21-085-H04-P, 5.5 contact hours; Infectious Diseases I, Infectious Diseases II, Neurology, General Psychiatry, and Fluids, Electrolytes, and Nutrition, Activity No. 0217-9999-21-086-H01-P, 5.75 contact hours; Critical Care, Anticoagulation, Endocrine and Metabolic Disorders, Oncology Supportive Care, and Gastrointestinal Disorders, Activity No. 0217-9999-21-087-H01-P, 5.5 contact hours; Geriatrics, Nephrology, and Pulmonary Disorders and Adult Immunizations, Activity No. 0217-9999-21-088-H04-P, 3.5 contact hours. All Pharmacotherapy Preparatory Review and Recertification Course sessions are application-based activities.

To earn continuing pharmacy education credit for the home-study version of the 2021 Pharmacotherapy Preparatory Review and Recertification Course, you must review all content and complete the attestation statements and course evaluations by May 17, 2024. Statements of continuing pharmacy education credit will be available at CPE Monitor within 2–3 business days after completion of this activity.

Board Certified Pharmacotherapy Specialist (BCPS) Recertification Credit
The Pharmacotherapy Preparatory Review and Recertification Course is part of a Board of Pharmacy Specialties (BPS)-approved professional development program for BCPS recertification credit. To be eligible to earn the 25.25 contact hours of pharmacotherapy recertification credit for the Pharmacotherapy Preparatory Review and Recertification Course, you must purchase and successfully submit the completed web-based posttest(s) by 11:59 p.m. (CDT) on May 17, 2022. To learn more about the Board of Pharmacy Specialties (BPS) specialty exams, please visit their website: www.bpsweb.org.

The American College of Clinical Pharmacy (ACCP) has compiled the materials in this course book for pharmacists to use in preparing for the Board of Pharmacy Specialties (BPS) Pharmacotherapy Specialty certification examination. There is no intent or assurance that all of the knowledge on the examination will be covered in the ACCP process. Although ACCP does use the BPS Content Outline in creating the material for this course, ACCP does not know the specific content of any particular BPS examination. BPS guidelines prohibit any overlap of individuals writing the examination and developing preparatory materials. To maintain its strict, independent standards for certification, BPS does NOT endorse or provide review information, preparatory courses, or study guides for Board Certification Examinations.

Program Goals and Target Audience

The Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Pharmacotherapy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of disease states and therapeutics;
2. To provide a framework to help attendees prepare for the specialty certification examination in pharmacotherapy; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each therapeutic area.

Faculty

Deborah S. Bondi, Pharm.D., BCPS, BCPPS
Clinical Pharmacy Coordinator – Pediatrics
Clinical Pharmacy Specialist – Neonatal Intensive Care Unit
University of Chicago Medicine, Comer Children's Hospital
Chicago, Illinois

Mary M. Bridgeman, Pharm.D., BCPS, BCGP
Clinical Professor
Ernest Mario School of Pharmacy
Rutgers University
Piscataway, New Jersey

John M. Burke, Pharm.D., FCCP, BCPS
Professor of Pharmacy Practice
Associate Dean for Post-Graduate Education
St. Louis College of Pharmacy
St. Louis, Missouri

Jacintha S. Cauffield, Pharm.D., BCPS, CDE, CRPS-A
Associate Professor of Pharmacy Practice
The Lloyd L. Gregory School of Pharmacy
Palm Beach Atlantic University
West Palm Beach, Florida

Paul P. Dobesh, Pharm.D., FCCP, BCPS, BCCP
Professor of Pharmacy Practice and Science
University of Nebraska Medical Center College of Pharmacy
Omaha, Nebraska

Christopher T. Elder, Pharm.D., BCOP
Assistant Professor of Pharmacy Practice
The Lloyd L. Gregory School of Pharmacy
Palm Beach Atlantic University
West Palm Beach, Florida

Shannon W. Finks, Pharm.D., FCCP, BCPS, BCCP, AHSCP-CHC
Professor of Clinical Pharmacy and Translational Science
University of Tennessee College of Pharmacy
Memphis, Tennessee

Caitlin M. Gibson, Pharm.D., BCPS, BCCP
Associate Professor
Vice Chair in Pharmacotherapy
University of North Texas System College of Pharmacy
Fort Worth, Texas

Leslie A. Hamilton, Pharm.D., FCCP, FCCM, BCPS, BCCCP
Associate Professor
University of Tennessee Health Science Center
Department of Clinical Pharmacy and Translational Science;
Neurocritical Care Clinical Specialist
University of Tennessee Medical Center
Knoxville, Tennessee

Brian K. Irons, Pharm.D., FCCP, BCACP
Professor of Pharmacy Practice
Texas Tech University Health Sciences Center
Jerry H. Hodge School of Pharmacy
Lubbock, Texas

Ashley H. Meredith, Pharm.D., FCCP, BCACP, BCPS, CDE
Clinical Associate Professor
Purdue University College of Pharmacy;
Clinical Pharmacy Specialist – Ambulatory Care
Eskenazi Health
Indianapolis, Indiana

Emily M. Scopelliti, Pharm.D., BCPS
Associate Professor – Department of Pharmacy Practice
Thomas Jefferson University
Philadelphia, Pennsylvania

Curtis L. Smith, Pharm.D., FCCP, BCPS
Professor
Ferris State University;
Clinical Pharmacist
Sparrow Health System
Lansing, Michigan

Kevin M. Sowinski, Pharm.D., FCCP
Professor of Pharmacy Practice
Purdue University College of Pharmacy;
Adjunct Professor of Medicine
Indiana University School of Medicine
Indianapolis, Indiana

Dustin D. Spencer, Pharm.D., MBA, BCPS, BCCP
Clinical Director
Cardinal Health
Martinsville, Indiana

Timothy E. Welty, Pharm.D., M.A., FCCP, FAES
Professor of Pharmacy Practice
Drake University;
Pharmacotherapy Specialist
Unity Point Neurology
Des Moines, Iowa

Sheila M. Wilhelm, Pharm.D., FCCP, BCPS
Clinical Professor
Wayne State University
Eugene Applebaum College of Pharmacy and Health Sciences
Detroit, Michigan

Corey J. Witenko, Pharm.D., BCPS, BCCCP
Clinical Pharmacy Manager
Director of PGY1 Pharmacy Residency Program
New York-Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

Faculty Disclosures

Consultant/Member of Advisory Board: Paul Dobesh (Pfizer/BMS Alliance, Janssen), Christopher T. Elder (BMS, GSK, AstraZeneca, Acceleron, Kyowa Kirin), Ashley H. Meredith (Birth Control Pharmacist, JACCP Editorial Board), Timothy E. Welty (Council on Clinical Activities, American Epilepsy Society)

Speaker's Bureau: Mary M. Bridgeman (AstraZeneca), Ashley H. Meredith (Surgent PharmCon)

Nothing to Disclose: Deborah S. Bondi, John M. Burke, Jacintha S. Cauffield, Shannon W. Finks, Caitlin M. Gibson, Leslie A. Hamilton, Brian K. Irons, Emily M. Scopelliti, Curtis L. Smith, Kevin M. Sowinski, Dustin D. Spencer, Sheila M. Wilhelm, Corey J. Witenko

Reviewer Disclosures

Employee: Jamie Danelo (Allergan through The Medical Affairs Company), Lori Gordon (ViiV Healthcare), Tenille L. Lawson (Eli Lilly and Co./Lilly Research Laboratories), Hany Mahmoud (Hoffmann-La Roche)

Nothing to Disclose: Elizabeth D. Bentley, Mikel K. Bofenkamp, Wayne E. Bradley, Clement Chung, Jeremy S. Daniel, Carley E. DeVee, Amber R. Douglass, Wasim S. El Nekidy, Shawn E. Fellows, Ashlee G. Hamel, Tudy M.R. Hodgman, Kelly C. Hoenig, Gregory J. Hughes, Jennifer E. Katzianer, Kristi W. Kelley, Christopher A. Knefelkamp, Chengqing Li, Evelina Lin, Claire A. Marten, Aimon C. Miranda, Donald C. Moore, Chelsea G. Owen, Peggy E. Pace, Elisabeth M. Palmer, Golden L. Peters, Jennifer L. Petrie, Brittany L. Riley, Angela A. Slampak-Cindric, Mary W. Subramanian, Nisha A. Tahiliani, Azita H. Talasaz, Donna M. Shuler Truoccolo, Mallory L. Turner, Edward Thomas Van Matre, Tyler A. Vest, Susan R. Winkler, Jessica B. Winter, Eman Elsayed Younis, Min Zhang, Gregory M. Zumach

Acknowledgments

Teresa M. Bailey, Pharm.D., BCPS
Professor
College of Pharmacy
Ferris State University
Big Rapids, Michigan

Debra J. Barnette, Pharm.D., BCPS
Assistant Professor of Clinical Pharmacy
Pharmacy Practice and Administration
Ohio State University College of Pharmacy
Columbus, Ohio

Deborah S. Bondi, Pharm.D., BCPS, BCPPS
Clinical Pharmacy Coordinator – Pediatrics
Clinical Pharmacy Specialist – Neonatal Intensive Care Unit
University of Chicago Medicine, Comer Children's Hospital
Chicago, Illinois

Lisa Anne Boothby, Pharm.D., BCPS
Clinical Research Pharmacist
Drug Information Coordinator
Pharmacy Administration
Columbus Regional Healthcare System
Columbus, Georgia

Linda R. Bressler, Pharm.D., BCOP
Clinical Associate Professor
Department of Pharmacy Practice
College of Pharmacy;
Director of Regulatory Affairs
Cancer and Leukemia Group B
University of Illinois
Chicago, Illinois

Mary M. Bridgeman, Pharm.D., BCPS, BCGP
Clinical Professor
Ernest Mario School of Pharmacy
Rutgers University
Piscataway, New Jersey

John M. Burke, Pharm.D., FCCP, BCPS
Professor of Pharmacy Practice
Associate Dean for Postgraduate Education
St. Louis College of Pharmacy
St. Louis, Missouri

Jacintha S. Cauffield, Pharm.D., BCPS, CDE, CRPS-A
Lloyd L. Gregory School of Pharmacy
Palm Beach Atlantic University
West Palm Beach, Florida

Sheryl Chow, Pharm.D., FCCP, BCPS-AQ Cardiology
Associate Professor of Pharmacy Practice and Administration
College of Pharmacy
Western University of Health Sciences
Los Angeles, California

G. Robert DeYoung, Pharm.D., BCPS
PGY1 Residency Program Director
Mercy Health Saint Mary's Campus;
Clinical Pharmacist
Mercy Health Physician Partners
Grand Rapids, Michigan

Paul Dobesh, Pharm.D., FCCP, BCPS-AQ Cardiology
Professor of Pharmacy Practice and Science
College of Pharmacy, University of Nebraska Medical Center
Omaha, Nebraska

Anna Legreid Dopp, Pharm.D.
Clinical Pharmacist
Drug Policy Program
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

Jennifer M. Dugan, Pharm.D., BCPS
Primary Care Clinical Pharmacy Specialist
Kaiser Permanente Colorado
Evergreen, Colorado

Christopher T. Elder, Pharm.D., BCOP
Assistant Professor of Pharmacy Practice
Lloyd L. Gregory School of Pharmacy, Palm Beach Atlantic University
West Palm Beach, Florida

Shareen El-Ibiary, Pharm.D., FCCP, BCPS
Professor of Pharmacy Practice
Department of Pharmacy Practice
Midwestern University College of Pharmacy-Glendale
Glendale, Arizona

Shannon W. Finks, Pharm.D., FCCP, BCPS
Professor
University of Tennessee College of Pharmacy
Clinical Pharmacy Specialist, Cardiology
Veterans Affairs Medical Center
Memphis, Tennessee

Edward F. Foote, Pharm.D., FCCP, BCPS
Professor
Wilkes University
Wilkes-Barre, Pennsylvania

Caitlin M. Gibson, Pharm.D., BCPS
Associate Professor
University of North Texas Health Science Center
Fort Worth, Texas

Miki Goldwire, MS, Pharm.D.
Assistant Professor
Regis University Rueckert-Hartman College for Health Professions
Denver, Colorado

Linda Gore Martin, Pharm.D., MBA, BCPS
Dean
Professor, Social and Administrative Pharmacy
University of Wyoming School of Pharmacy
Laramie, Wyoming

Leslie A. Hamilton, Pharm.D., FCCP, BCPS, BCCCP
Associate Professor
University of Tennessee Health Science Center
Department of Clinical Pharmacy and Translational Science;
Neurocritical Care Clinical Specialist
University of Tennessee Medical Center
Knoxville, Tennessee

Dana Hammer, Ph.D., Pharm.D.
Senior Lecturer and Director of Teaching Certificate Program in Pharmacy Education
Department of Pharmacy
University of Washington
Seattle, Washington

Ila M. Harris, Pharm.D., FCCP, BCPS
Associate Professor
Department of Family Medicine and Community Health
University of Minnesota;
Bethesda Family Medicine
St. Paul, Minnesota

Brian A. Hemstreet, Pharm.D., FCCP, BCPS
Assistant Dean for Student Affairs
Associate Professor
Regis University School of Pharmacy
Rueckert-Hartman College for Health Professions
Denver, Colorado

Tudy M.R. Hodgman, Pharm.D., FCCM, BCPS
Associate Professor of Pharmacy Practice
Clinical Coordinator/Critical Care Specialist
Northwest Community Hospital
Arlington Heights, Illinois

Lisa C. Hutchison, Pharm.D., MPH, FCCP, BCPS
Professor
Department of Pharmacy Practice
University of Arkansas for Medical Sciences
College of Pharmacy
Little Rock, Arkansas

Brian K. Irons, Pharm.D., FCCP, BCACP
Professor of Pharmacy Practice
Texas Tech University Health Sciences Center
Jerry H. Hodge School of Pharmacy
Lubbock, Texas

William A. Kehoe, Pharm.D., M.A., FCCP, BCPS
Professor, Department of Pharmacy Practice
Director of Student Academic Success
T.J. Long School of Pharmacy and Health Sciences
Stockton, California

Karen L. Kier, Ph.D., M.Sc., BCPS
Director of Assessment and Professor of Clinical Pharmacy
Ohio Northern University
Ada, Ohio

Mary Ann Kliethermes, Pharm.D.
Associate Professor
Chicago College of Pharmacy
Midwestern University
Downers Grove, Illinois

Judith Kristeller, Pharm.D., BCPS
Associate Professor
Wilkes University
Wilkes-Barre, Pennsylvania

Kelly C. Lee, Pharm.D., MAS, BCPP
Associate Professor of Clinical Pharmacy
Associate Dean for Assessment and Accreditation
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of California San Diego
La Jolla, California

Jamie L. McConaha, Pharm.D., BCACP
Assistant Professor of Pharmacy Practice
Duquesne University Mylan School of Pharmacy
Pittsburgh, Pennsylvania

Karen J. McConnell, Pharm.D., FCCP, BCPS-AQ Cardiology
Clinical Pharmacy Specialist
Cardinal Health;
Clinical Associate Professor
University of Colorado Skaggs School of Pharmacy
Denver, Colorado

John McGlew, M.A.
Director, Government Affairs
American College of Clinical Pharmacy
Washington, D.C.

Ashley H. Meredith, Pharm.D., BCPS, BCACP, CDE
Clinical Associate Professor
Purdue University, Department of Pharmacy Practice;
Clinical Pharmacy Specialist – Ambulatory Care
Eskenazi Health
West Lafayette, Indiana

LeAnn Norris, Pharm.D., BCPS, BCOP
Clinical Assistant Professor
Department of Clinical Pharmacy and Outcomes Sciences
South Carolina College of Pharmacy
Columbia, South Carolina

Kirsten H. Ohler, Pharm.D., BCPS
Pediatric Clinical Specialist
Florida Children's Hospital
Orlando, Florida

Norma J. Owens, Pharm.D., FCCP, BCPS
Professor and Chair
Pharmacy Department
University of Rhode Island
Providence, Rhode Island

Christopher A. Paciullo, Pharm.D., FCCP, FCCM, BCCCP
Manager, Decentralized Pharmacy Services
Emory University Hospital Midtown
Atlanta, Georgia

Robert Lee Page II, Pharm.D., FCCP, FAHA, BCPS
Associate Professor of Clinical Pharmacy and Physical Medicine
Schools of Pharmacy and Medicine
University of Colorado
Aurora, Colorado

Theresa R. Prosser, Pharm.D., BCPS
Professor
St. Louis College of Pharmacy
St. Louis, Missouri

Jo Ellen Rodgers, Pharm.D., FCCP, BCPS-AQ Cardiology
Associate Director, Clinical Fellowship Programs, DPET;
Clinical Associate Professor
School of Pharmacy
University of North Carolina
Chapel Hill, North Carolina

Melody Ryan, Pharm.D., BCPS
Associate Professor
Department of Pharmacy Practice and Science
College of Pharmacy, University of Kentucky
Lexington, Kentucky

Gordan S. Sacks, Pharm.D., FCCP, BCNSP
Department Head
Professor, Pharmacy Practice
Auburn University Harrison School of Pharmacy
Auburn, Alabama

Lisa A. Sanchez, Pharm.D.
President
PE Applications
Highlands Ranch, Colorado

Emily M. Scopelliti, Pharm.D., BCPS
Associate Professor – Department of Pharmacy Practice
Thomas Jefferson University
Philadelphia, Pennsylvania

Curtis L. Smith, Pharm.D., BCPS
Professor
Ferris State University;
Clinical Pharmacist
Sparrow Health System
Lansing, Michigan

Kevin M. Sowinski, Pharm.D., FCCP
Professor of Pharmacy Practice
Purdue University College of Pharmacy;
Adjunct Professor of Medicine
Indiana University School of Medicine
Indianapolis, Indiana

Anne P. Spencer, Pharm.D., FCCP, BCPS-AQ Cardiology
Associate Professor of Pharmacy and Clinical Sciences
College of Pharmacy
Medical University of South Carolina
Charleston, South Carolina

Dustin D. Spencer, Pharm.D., MBA, BCPS, BCCP
Clinical Director
Cardinal Health
Martinsville, Indiana

Ceressa T. Ward, Pharm.D., BCPS
Clinical Coordinator
Emory Crawford Long Hospital
Atlanta, Georgia

Timothy E. Welty, Pharm.D., M.A., FCCP, FAES
Professor of Pharmacy Practice
Drake University;
Pharmacotherapy Specialist
Unity Point Neurology
Des Moines, Iowa

Barbara S. Wiggins, Pharm.D., FCCP, FNLA, FAHA, BCPS, CLS, AACC
Clinical Pharmacy Specialist – Cardiology
Department of Pharmacy Services
Medical University of South Carolina;
Adjunct Associate Professor
South Carolina College of Pharmacy
Charleston, South Carolina

Sheila M. Wilhelm, Pharm.D., FCCP, BCPS
Clinical Professor
Wayne State University
Eugene Applebaum College of Pharmacy and Health Sciences
Detroit, Michigan

Corey J. Witenko, Pharm.D., BCPS, BCCCP
Clinical Pharmacy Manager
Director of PGY1 Pharmacy Residency Program
NewYork-Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

Eric T. Wittbrodt, Pharm.D., FCCP, BCPS
Principal Health Outcomes Liaison
Daiichi Sankyo, Inc.
Parsippany, New Jersey

Kristin Zimmerman, Pharm.D., BCACP, CGP
Associate Professor
Virginia Commonwealth University School of Pharmacy
Richmond, Virginia

Reviewers

The American College of Clinical Pharmacy and the authors would like to thank the following individuals for their reviews of the Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course.

Elizabeth D. Bentley, Pharm.D., MSJ, BCPS
Director of Clinical Pharmacy Services
Kaiser Permanente
Portland, Oregon

Mikel K. Bofenkamp, Pharm.D., BCPS
Pharmacist
Park Nicollet Methodist Hospital
Saint Louis Park, Minnesota

Wayne Ellis Bradley, Pharm.D., MBA, BCPS
Consultant
Johns Creek, Georgia

Clement Chung, Pharm.D., M.S., BCOP, BCPS
Oncology Clinical Pharmacy Specialist
Houston Methodist West Hospital
Houston, Texas

Jamie M. Danelo, Pharm.D., MBA/HCM, BCPS
Medical Science Liaison
Allergan through The Medical Affairs Company
Spokane, Washington

Jeremy S. Daniel, Pharm.D., BCPS, BCPP
Associate Professor of Pharmacy Practice
South Dakota State University College of Pharmacy and Allied Health Professions;
Psychiatric Clinical Pharmacist
Avera Behavioral Health Center
Sioux Falls, South Dakota

Carley E. DeVee, Pharm.D., BCPS
Clinical Pharmacy Specialist
Bristol Regional Medical Center
Bristol, Tennessee

Amber R. Douglass, Pharm.D., BCPS, BCPP
Clinical Pharmacy Specialist – Mental Health
Veterans Affairs
Nashville, Tennessee

Wasim S. El Nekidy, Pharm.D., BCPS, BCACP, BCIDP
Senior Pharmacotherapy Specialist
Cleveland Clinic Abu Dhabi;
Clinical Associate Professor of Medicine
Cleveland Clinic Learner College of Medicine of Case Western University
Abu Dhabi, United Arab Emirates

Shawn E. Fellows, Pharm.D., BCPS
Assistant Professor
Wegmans School of Pharmacy
Rochester, New York

Lori A. Gordon, Pharm.D., BCPS-AQ ID, AAHIVP
Medical Science Liaison
ViiV Healthcare
Brooklyn, New York

Ashlee G. Hamel, Pharm.D., BCPS
System Manager, Clinical Pharmacy Programs
Sentara Healthcare
Norfolk, Virginia

Tudy M.R. Hodgman, Pharm.D., FCCM, BCPS, BCCCP
Clinical Specialist Critical Care/Cardiology
TriStar Centennial Medical Center
Nashville, Tennessee

Kelly C. Hoenig, Pharm.D., BCPS
Clinical Pharmacy Specialist
University of Iowa Hospitals and Clinics
Iowa City, Iowa

Gregory J. Hughes, Pharm.D., BCPS, BCGP
Associate Clinical Professor
St. John's University
Queens, New York

Jennifer E. Katzianer, Pharm.D., BCPS
Clinical Coordinator
Johns Hopkins Home Care Group
Baltimore, Maryland

Kristi W. Kelley, Pharm.D., FCCP, BCPS, BCACP, BC-ADM, CDCES
Clinical Professor
Department of Pharmacy Practice Auburn University Harrison School of Pharmacy;
Clinical Pharmacist
Continuity of Care Internal Medicine Clinics – Brookwood Baptist Health
Birmingham, Alabama

Christopher A. Knefelkamp, Pharm.D., BCPS
Clinical Pharmacy Specialist
Richard L. Roudebush VA Medical Center
Indianapolis, Indiana

Tenille L. Lawson, Pharm.D., BCPS
Drug Information Specialist – Consultant
Indianapolis, Indiana

Chengqing Li, Pharm.D., M.S., BCPS, BCPP
Clinical Pharmacy Specialist
Facility Program Manager, Specialty Medications
Kansas City VA Medical Center
Kansas City, Missouri

Evelina Lin, Pharm.D., BCPS
Clinical Pharmacist
Loyola University Medical Center
Maywood, Illinois

Hany I. Mahmoud, BPharm, BCPS, PMP
Clinical Trial Manager
Roche
Saudi Arabia

Claire A. Marten, Pharm.D., BCPS
Clinical Pharmacy Specialist
University of Texas MD Anderson Cancer Center
Houston, Texas

Aimon C. Miranda, Pharm.D., BCPS
Associate Professor
University of South Florida TCOP
Tampa, Florida

Donald C. Moore, Pharm.D., BCPS, BCOP, DPLA
Pharmacist Clinical Coordinator – Hematology/Oncology
Levine Cancer Institute, Atrium Health
Concord, North Carolina

Chelsea G. Owen, Pharm.D., MPH, BCPS
Clinical Staff Pharmacist
Baptist Health Louisville
Louisville, Kentucky

Peggy E. Pace, Pharm.D., B.S., BCPS, BCGP
Clinical Pharmacist
Christian Hospital
St. Louis, Missouri

Elisabeth M. Palmer, Pharm.D., BCPS
Emergency Medicine Clinical Pharmacist
Banner Estrella Medical Center
Phoenix, Arizona

Golden L. Peters, Pharm.D., BCPS
Associate Professor
St. Louis College of Pharmacy;
Clinical Pharmacist
St. Louis County Department of Public Health
St. Louis, Missouri

Jennifer L. Petrie, Pharm.D., BCPS
Ambulatory Clinical Pharmacist
Cheyenne Regional Medical Center
Cheyenne, Wyoming

Brittany L. Riley, Pharm.D., M.S., BCPS
Associate Professor
Marshall University School of Pharmacy
Huntington, West Virginia

Angela A. Slampak-Cindric, Pharm.D., BCPS, BCCCP
Coordinator, Critical Care and Emergency Medicine
Director, PGY2 Critical Care Pharmacy Residency Program
Geisinger Medical Center
Danville, Pennsylvania

Mary W. Subramanian, Pharm.D., BCPS, BCPPS
Practice Lead – Pediatrics, PGY2 Pediatric RPD
Wake Forest Baptist Health
Winston-Salem, North Carolina

Nisha A. Tahiliani, Pharm.D., BCPS
Clinical Oncology Pharmacist
UF Health Jacksonville;
Clinical Assistant Professor
University of Florida College of Pharmacy
Jacksonville, Florida

Azita Haj Hossein Talasaz, Pharm.D., BCCP BCPS
Associate Professor, Clinical Pharmacy Specialist
Tehran Heart Center, Tehran University of Medical Sciences
Tehran, Iran

Donna M. Shuler Truoccolo, Pharm.D., BCPS, NHDP-BC
Emergency Medicine Clinical Pharmacist
UVA Health (University of Virginia Health System)
Charlottesville, Virginia;
Clinical Assistant Professor – Emergency Medicine
Virginia Commonwealth University School of Pharmacy
Richmond, Virginia

Mallory L. Turner, Pharm.D., BCPS
Professor
Harding University College of Pharmacy;
Clinical Pharmacist
Unity Health – White County Medical Center
Searcy, Arkansas

Edward T. Van Matre, Pharm.D., M.S., BCCCP
Assistant Professor
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee

Tyler A. Vest, Pharm.D., M.S., BCPS, BCSCP
Pharmacy Manager, Automated Dispensing Cabinetry and Controlled Substances
Duke University Hospital
Durham, North Carolina;
Assistant Professor of Clinical Education
UNC Eshelman School of Pharmacy
Chapel Hill, North Carolina

Susan R. Winkler, Pharm.D., FCCP, BCPS
Department Chair and Professor, Pharmacy Practice
Midwestern University College of Pharmacy, Downers Grove Campus
Downers Grove, Illinois

Jessica B. Winter, Pharm.D., BCPS, BCCCP
Clinical Pharmacy Specialist, Emergency Medicine/Critical Care
University of Cincinnati Medical Center;
Adjunct Clinical Professor
University of Cincinnati College of Pharmacy
Cincinnati, Ohio

Eman E. Younis, Pharm.D., B.S., BCPS-AQ Cardiology
Senior Clinical Pharmacist
Saudi German Hospital Group-Madinah
Madinah, Saudi Arabia

Min Zhang, Pharm.D., BCPS
Clinical Pharmacy Specialist
Boston Medical Center;
Affiliate Assistant Professor
School of Pharmacy, Northeastern University
Boston, Massachusetts

Gregory M. Zumach, Pharm.D., BCPS
Clinical Assistant Professor
Oregon State University;
Clinical Pharmacist
Good Samaritan Regional Medical Center
Corvallis, Oregon

Table of Contents (Volume 2)

General Psychiatry **2-1**
Schizophrenia; Major Depressive Disorder (MDD); Bipolar Disorder; Anxiety and Related Disorders (OCD, PTSD); Insomnia; Substance Use Disorders

Fluids, Electrolytes, and Nutrition **2-73**
Fluid Management; Osmolality; Hypertonic Saline; Hypotonic Intravenous Fluids; Hyponatremia and Hypo-osmolal States; Hypernatremia and Hyperosmolal States; Disorders of K^+; Disorders of Magnesium Homeostasis; Disorders of Phosphorus Homeostasis; Disorders of Calcium Homeostasis; Enteral Nutrition; Parenteral Nutrition

Critical Care **2-127**
Interpretation of Hemodynamic Parameters; Treatment of Shock; Interpretation of Acid-Base Disturbances; Acute Respiratory Failure; Cardiac Arrest; Pain, Agitation, Delirium, and Neuromuscular Blockade; Glucose Control; Preventing Stress Ulcers; Pharmacologic Therapy for Preventing Venous Thromboembolism; Preventing Ventilator-Associated Pneumonia; Nutrition Support in Critically Ill Patients; Intracranial Hemorrhage

Anticoagulation **2-187**
Stroke Prevention in Nonvalvular Atrial Fibrillation; Anticoagulation in Valvular Disease; Prevention of Venous Thromboembolism; Treatment of Venous Thromboembolism; Reversal of Anticoagulation

Endocrine and Metabolic Disorders **2-241**
Thyroid Disorders; Pituitary Gland Disorders; Adrenal Gland Disorders; Obesity; Polycystic Ovary Syndrome; Diabetes Mellitus; Treatment of Diabetes Mellitus Complications; Other Diabetes Medication Issues; Diabetes Insipidus

Oncology Supportive Care **2-299**
Antiemetics; Pain Management; Treatment of Febrile Neutropenia; Use of Colony-Stimulating Factors for Prevention of Febrile Neutropenia; Thrombocytopenia; Anemia and Fatigue; Chemoprotectants; Oncologic Emergencies; Miscellaneous Antineoplastic Pharmacotherapy

Gastrointestinal Disorders **2-345**
Gastroesophageal Reflux Disease (GERD); Peptic Ulcer Disease; Upper GI Bleeding; Inflammatory Bowel Disease (IBD); Complications of Liver Disease; Viral Hepatitis; Nausea and Vomiting; Pancreatitis; Diarrhea; Constipation; Irritable Bowel Syndrome

Geriatrics **2-433**
Optimizing Pharmacotherapy in Older Adults; Dementia; Behavioral and Psychological Symptoms of Dementia; Urinary Incontinence; Benign Prostatic Hypertrophy; Osteoarthritis; Rheumatoid Arthritis; Gout

Nephrology 2-483
Acute Kidney Injury or Acute Renal Failure; Drug-Induced Kidney Damage; Chronic Kidney Disease; Renal Replacement Therapy; Managing the Complications of Chronic Kidney Disease; Dosage Adjustments in Kidney Disease

Pulmonary Disorders and Adult Immunizations 2-531
Asthma; Chronic Obstructive Pulmonary Disease; Adult Immunizations

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General Psychiatry

Jacintha Cauffield, Pharm.D.,
BCPS, CDCES, CRPS-A

Palm Beach Atlantic University
Lloyd L. Gregory School of Pharmacy
West Palm Beach, Florida

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Learning Objectives

1. Examine pharmacotherapeutic options for managing schizophrenia, major depressive disorder (MDD), bipolar disorder, anxiety and anxiety-like disorders, insomnia, and substance use disorders (SUDs).
2. Select a drug used to treat these disorders on the basis of its unique pharmacologic properties, therapeutic efficacy, adverse effects, and cognitive and behavioral effects.
3. Formulate a pharmacotherapeutic treatment plan for a patient with a diagnosis of schizophrenia, MDD, bipolar disorder, anxiety and anxiety-like disorders, insomnia, or SUD.

Abbreviations in This Chapter

APA	American Psychiatric Association
CBT	Cognitive behavioral therapy
CNS	Central nervous system
CYP	Cytochrome P450 enzyme system
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EPS	Extrapyramidal symptoms
FGA	First-generation antipsychotic
GAD	Generalized anxiety disorder
LAI	Long-acting injectable
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NMS	Neuroleptic malignant syndrome
OCD	Obsessive-compulsive disorder
OH	Orthostatic hypotension
OUD	Opioid use disorder
PTSD	Posttraumatic stress disorder
REM	Rapid eye movement
REMS	Risk Evaluation and Mitigation Strategies
SAMHSA	Substance Abuse and Mental Health Services Administration
SGA	Second-generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder
TCA	Tricyclic antidepressant

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 36-year-old man presents with a 16-year history of schizophrenia and alcohol use disorder. His medication was recently changed from haloperidol to aripiprazole because of gynecomastia and impotence. Today, he is pacing in your office and seems anxious and agitated. He has not been sleeping well and feels uncomfortable in his skin. Which medication would be most appropriate to help relieve this patient's symptoms?
   A. Benztropine.
   B. Dantrolene.
   C. Lorazepam.
   D. Propranolol.

2. A 52-year-old woman (body mass index [BMI] 35 kg/m^2) with schizophrenia presents for a routine follow-up. She is noted to have abnormal repetitive chewing type movements in her jaw, which she seems unable to control. She states that they are bothersome and interfere with her ability to eat, and she stays home because she is ashamed to be seen in public. She has taken perphenazine for the past 8 years with good control of her symptoms. She is able to live independently and care for herself. She did not respond to therapeutic trials of aripiprazole, ziprasidone, or haloperidol. She has gained 22.7 kg (50 lb) and developed type 2 diabetes while taking olanzapine. The diabetes resolved off olanzapine. Which would be the best treatment?
   A. Add benztropine.
   B. Add lorazepam.
   C. Change to quetiapine.
   D. Add valbenazine.

3. A 67-year-old man is admitted for new-onset tonic-clonic seizures. His medical history is negative for seizure disorders but positive for prediabetes and schizophrenia. His schizophrenia has been stabilized on clozapine 900 mg daily for many years. He also takes diphenhydramine 50 mg at bedtime, metformin 1000 mg twice daily, and bupropion extended release (ER) 300 mg daily (for 2 months).

His social history is negative for alcohol and illicit drug use but positive for a 25 pack-year history, which he stopped 2 weeks ago. Which medication is most likely responsible for his seizures?

A. Bupropion.
B. Clozapine.
C. Diphenhydramine.
D. Metformin.

4. A 25-year-old woman presents to your practice with a depressed mood that has worsened during the past few weeks. She finds it difficult to get out of bed in the morning. When she is not sleeping, she is eating. She has gained 4.5 kg (10 lb) in the past month. She is worried about her job and does not feel that she is "pulling her weight," even though she recently received a glowing evaluation. She has passive thoughts of harming herself but no definite plan. Her medical history includes anxiety, gastroesophageal reflux disease, and hypothyroidism (thyroid-stimulating hormone [TSH] within normal limits). She currently takes levothyroxine 100 mcg daily, lansoprazole 30 mg every morning, and alprazolam 0.5 mg three times daily for anxiety. Which medication would best treat her symptoms?

A. Desipramine.
B. Fluoxetine.
C. Mirtazapine.
D. Paroxetine.

5. A 56-year-old woman presents with a medical history significant for recurrent major depression and type 2 diabetes with newly diagnosed neuropathy, obesity, and coronary artery disease. She takes citalopram 40 mg daily, carvedilol 25 mg twice daily, lisinopril 40 mg daily, and metformin 1000 mg twice daily. She is tearful during her appointment and continues to have symptoms of depression despite initial improvement with citalopram. She wants to change antidepressants. Which would be most beneficial?

A. Bupropion.
B. Duloxetine.
C. Nortriptyline.
D. Sertraline.

6. A 45-year-old man presents with agitation and diaphoresis and an oral temperature of 38.5°C (101.3°F). His right eyelid began twitching about an hour ago, and he cannot make it stop. He developed cold symptoms 2 days ago and began taking dextromethorphan and pseudoephedrine around-the-clock. His medical history includes depression, hypertension, and dyslipidemia. He takes cetirizine 10 mg at bedtime, paroxetine 40 mg at bedtime, diltiazem extended release (XR) 240 mg daily, and rosuvastatin 10 mg daily. Which combination of medications is most likely contributing to his current symptoms?

A. Cetirizine and paroxetine.
B. Dextromethorphan and pseudoephedrine.
C. Diltiazem and pseudoephedrine.
D. Paroxetine and dextromethorphan.

7. A 31-year-old man presents with a 5-year history of type I bipolar disorder, for which he takes lithium 300 mg twice daily. He has been adherent to treatment. His lithium serum concentration, obtained yesterday before his morning lithium dose, is 1.0 mEq/L. He has been without manic symptoms for the past few years. He is admitted for a suicide attempt using acetaminophen. For the past few weeks, he has lost interest in his job and isolated himself from other people. Which medication would best help his acute symptoms?

A. Aripiprazole.
B. Lamotrigine.
C. Quetiapine.
D. Venlafaxine.

8. A 28-year-old woman (height 61 inches, weight 74.8 kg [165 lb], up from 68 kg [150 lb] 2 months ago) presents with a history of type I bipolar disorder. She has taken lithium 450 mg twice daily for the past 6 months. Her last serum concentration (3 months ago) was 0.7 mEq/L. She presents today for an annual examination. Her laboratory test results include sodium (Na) 138 mEq/L, potassium (K) 4.7 mEq/L, serum creatinine (SCr) 0.9 mg/dL, glucose 124 mg/dL, and TSH 24 mIU/mL. Additional medications include olanzapine 10 mg at bedtime (for 1 year), ethinyl estradiol/drospirenone (Yasmin)

daily, and a multivitamin. Which laboratory finding is most closely associated with her current medication regimen?

A. Glucose.
B. SCr.
C. Na.
D. TSH.

9. A 43-year-old woman presents with right upper quadrant abdominal pain with rebound tenderness, nausea, and vomiting. Her medical history is significant for rapid-cycling bipolar disorder, hypertension, obesity, and asthma. She takes divalproex sodium 500 mg twice daily, lamotrigine 150 mg twice daily, aripiprazole 30 mg daily, ramipril 10 mg daily, albuterol hydrofluoroalkane (HFA) 2 puffs every 6 hours, and fluticasone/salmeterol dry powder inhaler 250/50 twice daily. She started a prednisone taper 3 days ago for an asthma exacerbation. Laboratory test results include sodium 141 mEq/L, potassium 3.3 mEq/L, chloride 95 mEq/L, carbon dioxide 26 mmol/L, SCr 1.0 mg/dL, glucose 72 mg/dL, total cholesterol 165 mg/dL, triglycerides 188 mg/dL, aspartate aminotransferase (AST) 27 U/L, alanine aminotransferase (ALT) 21 U/L, amylase 456 U/L, lipase 387 U/L, and valproic acid trough concentration 56 mg/dL. Which medication is most likely responsible for her current clinical picture?

A. Aripiprazole.
B. Divalproex sodium.
C. Lamotrigine.
D. Prednisone.

10. A 20-year-old woman presents to the emergency department after experiencing trembling, sweating, chest pain, and shortness of breath accompanied by intense fear. A myocardial infarction has been ruled out. She has been given a diagnosis of panic disorder. In addition to a medication for her acute symptoms, which medication would provide the best long-term control?

A. Alprazolam.
B. Buspirone.
C. Hydroxyzine.
D. Paroxetine.

11. A 55-year-old woman presents with uncontrolled generalized anxiety disorder (GAD). Concomitant medical conditions include a history of breast cancer, dyslipidemia, osteoarthritis, vasomotor symptoms, and osteopenia. She takes tamoxifen, simvastatin, ibuprofen, lorazepam, and alendronate. Her physician would like her to have better control of her anxiety symptoms. He would also like to taper off lorazepam. Her GAD has not been controlled with paroxetine, sertraline, or duloxetine. Which agent would be best?

A. Bupropion.
B. Fluoxetine.
C. Pregabalin.
D. Venlafaxine.

12. A 74-year-old woman has difficulty getting to sleep. Once she falls asleep, she rests comfortably throughout the night. She has struggled with keeping a consistent bedtime for the past few months. She has no identifiable contributing factors. Concomitant medical conditions include hypertension, arthritis, and mild cognitive impairment. She has tried diphenhydramine but states that it helped for only a few nights and "made me loopy." She would like a medication with the least risk of hangover effect. Which medication is best?

A. Eszopiclone.
B. Ramelteon.
C. Suvorexant.
D. Zolpidem.

13. A 23-year-old man has a history of heroin addiction. He has successfully been maintained on methadone 40 mg daily for 1 year. He would like an option that does not require him to go to a daily opioid treatment program to get his methadone dose. He is not taking other medications, nor does he abuse other substances. Which treatment regimen is most appropriate?

A. Initiate supervised buprenorphine/naloxone.
B. Change to buprenorphine × 2 days; then take buprenorphine/naloxone.
C. Change to naltrexone.
D. Taper to methadone 30 mg; then change to buprenorphine.

14. A 55-year-old man has a 30-year history of alcohol dependence. He drinks 1 pint of vodka daily. He has tried several times to quit without success. He recently reconciled with his estranged son and wants to be sober so that he can be present in his son's life. His medical history includes heroin use, depression, and posttraumatic stress disorder (PTSD). Concomitant medications include methadone maintenance (which he wishes to continue) and sertraline (currently nonadherent). His liver function test results include AST 143 U/L, ALT 74 U/L, albumin 4.0 g/dL, alkaline phosphatase 75 U/L, total bilirubin 0.3 mg/dL, prothrombin time 15.1 seconds, international normalized ratio 0.9, platelet count 370,000/mm^3, and creatinine clearance (CrCl) 40 mL/minute/1.73 m^2. After alcohol detoxification, which maintenance treatment is most appropriate?

    A. Acamprosate 333 mg three times daily.

    B. Chlordiazepoxide 25 mg four times daily.

    C. Disulfiram 500 mg daily.

    D. Naltrexone 50 mg daily.

15. A 44-year-old man is preparing to be discharged from the hospital after a myocardial infarction. He has a 25 pack-year history of smoking cigarettes and smokes 1½ packs/day. He has unsuccessfully tried to quit twice. He tried quitting "cold turkey" the first time about 5 years ago. He resumed smoking 6 months later when he lost his job. He tried again about 6 months ago using the 2-mg strength of nicotine gum. To save money, he chewed 7 pieces daily. He has just been given a diagnosis of depression. Which regimen would be best?

    A. Bupropion suspended release (SR).

    B. Nicotine gum.

    C. Nicotine patch.

    D. Varenicline.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 1: a-q
    b. Task 2: a-d
    c. Task 3: a-g
    d. Task 4: a-d
    ed. Task 5: a-e

Patient Case

Questions 1–4 pertain to the following case.

A 25-year-old man (BMI 35 kg/m^2) has recently diagnosed schizophrenia. He often hears voices telling him that he is "stupid and worthless" and that he should "just jump off the roof of his apartment building." His parents became very concerned about his isolative behavior and brought him to the hospital. He was given haloperidol in the psychiatry unit and now presents with neck stiffness and in oculogyric crisis. Until now, he has not taken medications because he thought he could control his symptoms on his own with vitamins and energy drinks, though he has difficulty remembering to take these. He has an additional history of marijuana and alcohol use disorders.

1. Which is most appropriate for this patient's symptoms at this time?
   A. Benztropine.
   B. Dantrolene.
   C. Lorazepam.
   D. Propranolol.

2. He is initiated on aripiprazole. Which is the best rationale for this selection, given patient-specific factors?
   A. Aripiprazole has no risk of causing extrapyramidal symptoms (EPS).
   B. Aripiprazole is available in a long-acting injection (LAI) to increase adherence.
   C. Aripiprazole would eliminate this patient's negative symptoms.
   D. Aripiprazole is effective against substance use disorders.

3. Which is the best example of an adverse effect of aripiprazole that would be of concern when initiated in this patient?
   A. Sedation.
   B. Anticholinergic effects.
   C. Akathisia.
   D. Corrected QT (QTc) prolongation.

4. One year later, he no longer responds to aripiprazole, and you decide to change his medication. He is only interested in oral medications. Given this patient's history, which agent is most appropriate at this time?
   A. Clozapine.
   B. Fluphenazine.
   C. Olanzapine.
   D. Ziprasidone.

I. SCHIZOPHRENIA

A. Characteristics

1. Schizophrenia is a disorder involving psychosis and a complex mix of symptoms. The *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-5*) identifies five symptoms for diagnosis. At least two of the following symptoms must be present for at least 1 month, and at least one of the symptoms should be delusions, hallucinations, or disorganized speech. Continuous signs of disturbance must be present for at least 6 months.

a. Delusions: Fixed false beliefs involving misinterpretations of reality that are resistant to evidence refuting them. Trying to dispel a delusion can undermine therapeutic alliance. Examples include persecutory (e.g., someone is going to get me), paranoid (e.g., someone is watching), and command (e.g., someone told me to do it).
b. Hallucinations: Perceptual abnormalities that can involve any sensory system. Auditory hallucinations are the most common.
c. Disorganized speech: This manifests as frequent "derailment" of speech or incoherence.
    i. "Loose associations:": Going from one unrelated topic to another as though the topics were connected
    ii. "Tangential" speech refers to answers to questions that are only slightly related or that are totally unrelated to the question.
    iii. "Word salad" refers to speech that is almost incomprehensible and is very much like receptive aphasia.
d. Grossly disorganized or catatonic behavior
e. Negative symptoms (Table 1)

2. Schizophrenia can be divided into positive, negative, and cognitive symptoms (see Table 1).
3. Anosognosia: Many patients (57%–98%) with schizophrenia may lack awareness of or insight into their illness. Anosognosia may or may not improve with treatment. It is the most common predictor of nonadherence and predicts higher relapse rates, more involuntary treatments, poorer psychosocial functioning, aggression, and a poorer course of illness.

Table 1. Categories of Schizophrenia-Associated Signs and Symptoms

Positive (presence of something that should not be there)	**Negative (absence of something that should be present)**	**Cognitive**
Antipsychotics are most effective against these	**Antipsychotics may not be completely effective**	**No current medications effectively treat these**
Hallucinations[a]	Blunted or flat affect[a]	Poor executive function
Delusions[a]	Social withdrawal (passive-apathetic)[a]	Impaired attention
Paranoia or suspiciousness[a]	Lack of personal hygiene	Impaired working memory (does not learn from mistakes)
Conceptual disorganization[a,b]	Prolonged time to respond[a]	
Hostility[a]	Poor rapport[a]	
Grandiosity[a]	Poor abstract thinking[a]	
Excitement[a]	Poverty of speech (lack of spontaneity and flow of conversation)[a]	
Loose associations	Emotional withdrawala	
Thought broadcasting	Alogia (poverty of speech)	
Thought insertion	Ambivalence (simultaneous, contradictory thinking); prevents decision-making	
	Asociality; internally directed	
	Amotivation (avolition)	
	Anhedonia	

[a]These symptoms are used to score the positive and negative portions of the Positive and Negative Syndrome Scale (PANSS).

[b]Conceptual disorganization, according to the Brief Psychiatric Rating Scale (BPRS), is the "degree to which speech is confused, disconnected, vague or disorganized." This includes tangential thinking, circumstantiality, sudden topic shifts, incoherence, derailment, blocking, neologisms, clanging, word salad, and other speech disorders.

B. Course of Illness
   1. Onset is usually between adolescence and early adulthood. Schizophrenia occurs earlier in men (i.e., early 20s) than in women (i.e., late 20s to early 30s). The prevalence is around 1.1% and is equal between the sexes.
   2. Most patients fluctuate between acute episodes and remission. Residual symptoms may present between episodes.
   3. The lifetime course of schizophrenia has four phases: prodromal, acute, stabilization, and stable.
      a. Prodromal: This phase is characterized by the gradual development of symptoms that may go unnoticed until a major positive symptom occurs. This phase may include isolation, deterioration of hygiene, loss of interest in work or school, and dysphoria.
      b. Acute: Clinically significant positive symptoms are present, often requiring hospitalization. Patients may be unable to care for themselves during this phase.
      c. Stabilization: The acute symptoms begin to decrease, and this phase may last for several months.
      d. Stable: During this phase, positive symptoms have markedly declined and may not be present. Negative symptoms may resolve. Cognitive symptoms may be present. Nonpsychotic symptoms such as anxiety and depression may be present.
   4. Complete remission without symptoms is uncommon.

C. Causes
   1. The causes of schizophrenia are unknown. Schizophrenia appears to involve neurophysiologic and psychological abnormalities.
   2. The primary neurotransmitters believed to be involved in the cause are dopamine and serotonin. The exact relationship between these neurotransmitters remains unknown. In some areas of the brain, dopamine overactivity appears to result in some symptoms, whereas in others, underactivity may occur. Glutamatergic receptor dysfunction may also play a role in causing schizophrenia. Glutamate is associated with several processes that involve cognition, memory, and perception.
   3. Many potential risk factors for schizophrenia have been identified, including a family history of schizophrenia, perinatal trauma (e.g., hypoxia, fetal distress, influenza, and nutritional deficiencies), obstetric complications, living in an urban area, having stress, and being born during the winter.

D. Rating Scales
   1. The Brief Psychiatric Rating Scale (BPRS), developed in 1962, is a general psychiatric rating scale that has been used to measure outcomes in clinical trials, including those involving schizophrenia.
   2. The Positive and Negative Syndrome Scale (PANSS) is a 30-item, 7-point scale that was partly adapted from the BPRS. The PANSS is considered the gold standard and is widely used to evaluate antipsychotic therapy in clinical trials but not in daily clinical practice. This scale requires a 45-minute interview with the patient. The interviewer must be specially trained to administer it.
   3. The PANSS-6 is a scalable abbreviated version of the PANSS that can be used clinically. It consists of the following components: P1-Delusions, P2-Conceptual disorganization, P3-Hallucinations, N1-Blunted Affect, N4-Social withdrawal, and N6-Lack of spontaneity and flow of conversation. It is sensitive to changes in treatment. A score of less than 14 signifies remission.

E. Antipsychotics
   1. First-line agents for treating schizophrenia
   2. Two classes
      a. First-generation antipsychotics (FGAs; also called typical or conventional antipsychotics; Table 2). These include all the older antipsychotics. Chlorpromazine, a phenothiazine, was the first to be used clinically.

Table 2. FGAs for Schizophrenia

Agent	Dose Equivalent (mg)	Potency[a]	Anticholinergic	Sedation	Orthostatic Hypertension	Extrapyramidal Symptoms
Chlorpromazine[b]	100	Low	+++	++++	+++	++
Fluphenazine[b]	2	High	+	+	+	+++
Haloperidol	2	High	+	+	+	+++
Loxapine	10	Int.	++	++	++	++
Molindone	—	—	+	++	+	++
Perphenazine[b]	10	Int.	++	++	++	++
Pimozide	2	High	+	+	+	+++
Thioridazine[b]	100	Low	+++	+++	+++	+
Thiothixene	4	High	+	+	+	+++
Trifluoperazine[b]	5	Int	++	+	+	++

[a]Potency = D_2 receptor affinity.

[b]Phenothiazine.

Int. = intermediate.

i. These agents can be categorized according to potency as antagonists at the dopamine D_2 receptors, which are thought to be the mechanism of pharmacologic activity, particularly in the mesolimbic areas of the brain for treating psychotic symptoms. Blockade in the mesocortical areas may worsen negative and cognitive symptoms. Potency at the D_2 receptors can be split into low, intermediate, and high. FGAs can be interconverted using chlorpromazine dose equivalents.

ii. Adverse effect profiles also differ by potency and are relatively uniform for agents with similar dopamine potency.

(a) Low potency: Concomitant anticholinergic, antihistaminic, and α-adrenergic blocking properties are also present.

(b) High potency: Less potency at the other receptors; dopamine-related adverse effects, including extrapyramidal symptoms (EPS) and hyperprolactinemia, tend to be the main adverse effects and are more prevalent than with low-potency agents.

(c) Sedation: More common with low-potency agents. Sedation is usually worse initially and then better tolerated with time. Sedation tends to be dose related.

(d) Anticholinergic effects: More common with low-potency agents. Dry mouth, constipation, blurred vision, and urinary hesitancy can occur. Dose-dependent.

(e) Orthostatic hypotension (OH): More common with low-potency agents because of blockade of the α-adrenergic receptor.

b. Second-generation antipsychotics (SGAs; also called atypical antipsychotics; see Table 3): These include the newer agents, beginning with clozapine. The adverse effect profile of SGAs is more heterogeneous and differs from that of FGAs.

Table 3. SGAs for Schizophrenia

Drug (generic/ brand)	Metabolic Syndrome			Anticholinergic	Sedation	Orthostasis	Extrapyramidal Symptoms	
	Weight Gain	Glucose Abnormality	Dyslipidemia				Akathisia	Parkinsonism
Aripiprazole (Abilify)	+	+	+	+	+	+	++	+
Asenapine (Saphris)	++	++	++	+	++	++	++	+
Brexpiprazole (Rexulti)	+	+	++	+	++	+	++	+
Cariprazine (Vraylar)	++	+	+	++	++	++	++	+
Clozapine (Clozaril)	+++	+++	+++	+++	+++	+++	+	+
Iloperidone (Fanapt)	++	++	+	+	+	+++	+	+
Lumateperone (Caplyta)	+	-	-	+	+	+	-	-
Lurasidone (Latuda)	+	++	++	+	+	+	++	++
Olanzapine (Zyprexa)	+++	+++	+++	++	++	++	++	++
Paliperidone (Invega)	++	+	++	+	+	++	++	++
Quetiapine (Seroquel)	++	++	+++	++	+++	++	+	+
Risperidone (Risperdal)	++	++	+	+	++	++	++	++
Ziprasidone (Geodon)	+	+	+	+	++	++	++	+

i. SGAs (or atypical antipsychotics) were developed to reduce EPS adverse effects and tardive dyskinesia and to improve efficacy. The characteristics that define "atypicality" are not all agreed on, but in general, they all share at least three characteristics:
   (a) The risk of EPS is lower than with typical antipsychotics at usual clinical doses,
   (b) The risk of tardive dyskinesia is reduced, and
   (c) The ability to block serotonin-2 receptors is present. This third property may improve the negative symptoms of schizophrenia and reduce the risk of EPS. This may also be related to SGA efficacy in mood disorders.

ii. Some unique mechanisms exist among individual SGAs that may influence the effects on symptoms of schizophrenia:
   (a) Some low-potency SGAs, including quetiapine and clozapine, have faster dissociation/ weaker affinity binding at D_2 receptors.
   (b) Some SGAs have partial agonism at D_2 receptors (aripiprazole, brexpiprazole, cariprazine). This may stabilize dopamine transmission by reducing D_2 hyperactivity in the mesolimbic neurons.
   (c) Cariprazine has high potency at D_3 receptors, with may confer some benefit against negative and cognitive symptoms.

(d) Many SGAs have partial activity at serotonin-1A receptors. This may increase the release of dopamine in the prefrontal cortex, which may benefit cognition. It may also decrease EPS and improve mood. Clozapine, quetiapine, and ziprasidone have some serotonin-1A activity, but aripiprazole, brexpiprazole, and cariprazine appear to have more potent activity.

iii. Many clinicians see SGAs as first-line agents, likely because of the decreased risk of tardive dyskinesia and EPS. SGAs (particularly clozapine and olanzapine) have been associated with new-onset diabetes and metabolic syndrome. All patients prescribed SGAs should be monitored for BMI, blood pressure, fasting glucose, lipids (TG, HDL), and waist circumference at baseline and periodically thereafter according to the American Psychiatric Association (APA)/American Diabetes Association (ADA) consensus recommendations.

F. Adverse Effects of Antipsychotics

1. All antipsychotics carry a black box warning against use in older adults with dementia. FGAs may have a higher mortality rate than SGAs when used in older adults with dementia.
2. Some antipsychotics indicated for the treatment of mood disorders (particularly depression) carry a black box warning for an increased risk of suicidal thoughts and behavior in children, adolescents, and young adults (24 years and younger) similar to antidepressants (see the MDD section in the text that follows for more details). The antipsychotics included in this warning are aripiprazole, brexpiprazole, cariprazine, lurasidone, and quetiapine.
3. EPS: Can occur with all antipsychotics, but are most common among the FGAs, particularly the high-potency agents. EPS are thought to result from blockade of D2 receptors in the nigrostriatal pathway. There are four main manifestations:
   a. Pseudoparkinsonism: This is manifested by symptoms such as bradykinesia, rigidity, tremor, or akinesia. If possible, the dose of the antipsychotic should be lowered or the patient changed to another antipsychotic with less possibility of causing parkinsonism. If neither is possible, parkinsonism is usually responsive to anticholinergic agents such as diphenhydramine, trihexyphenidyl, and benztropine.
   b. Dystonia: These episodes are often acute. The risk is greatest in young men and with high doses of parenteral antipsychotics. Examples include torticollis, laryngospasm, and oculogyric crisis. Acute dystonia is treated with intramuscular anticholinergics. Dystonias are treated with oral anticholinergics.
   c. Akathisia: This is a somatic restlessness and inability to stay still or calm. Reducing the antipsychotic dose and changing to an agent with a lower incidence of akathisia are the best options, but these are not always feasible. Akathisia responds poorly to anticholinergics. Lipophilic (fat soluble) β-blockers such as propranolol are typically used. Data analyses for efficacy are inconclusive, but β-blockers are commonly used in practice. Benzodiazepines can also be used to treat akathisia but are considered second line behind β-blockers.
   d. Tardive dyskinesia: Characterized by abnormal involuntary movements that occur with long-term antipsychotic therapy. Tardive dyskinesia usually involves the orofacial muscles and is often insidious. With continued drug exposure, particularly at high doses, tardive dyskinesia is often irreversible. Risks are likely related to the total cumulative dose. Those taking high antipsychotic doses, those older than 54 years, women, and those with mood disorders are also at an increased risk. Symptoms may decrease with lowering the antipsychotic dose (after an initial symptom increase). However, this dose reduction must be weighed against worsening symptoms of schizophrenia. Changing to an agent that is associated with less tardive dyskinesia is also an option. The risk is higher with FGAs than with SGAs. Clozapine has not been associated with tardive dyskinesia, and changing to this drug may be appropriate for patients with moderate to severe symptoms.

The other atypical antipsychotics also appear to have a low potential to cause tardive dyskinesia. Patients taking antipsychotics should be monitored at least annually using a rating scale, such as AIMS (Abnormal Involuntary Movement Scale) or DISCUS (Dyskinesia Identification System Condensed User Scale).

i. Valbenazine (Ingrezza) and deutetrabenazine (Austedo) are both U.S. Food and Drug Administration (FDA) approved as the first drugs to carry an indication for tardive dyskinesia. The exact mechanism of action is unknown, but both agents reversibly and selectively inhibit the vesicular monoamine transporter 2 (VMAT2). They thus regulate the packaging of dopamine and other monoamines in the neuronal cytoplasm into vesicles for storage and release into synapses, decreasing the dopamine released, which results in fewer postsynaptic dopamine receptors and less dyskinetic movement. Valbenazine is dosed once daily, which must be adjusted for strong 3A4 and 2D6 inhibitors. Deutetrabenazine is dosed twice daily, which must be adjusted for strong 2D6 inhibitors. Adverse effects of both include sleepiness, depression, and QT prolongation. Deutetrabenazine carries a black box warning regarding increased risk of suicidality. Tetrabenazine, a VMAT2 inhibitor indicated for the treatment of chorea associated with Huntington disease, is also used off-label for tardive dyskinesia.

ii. Anticholinergic agents should not be given to treat tardive dyskinesia and may in fact worsen the symptoms.

4. Neuroleptic malignant syndrome (NMS): Occurs with all agents but is more common with high-potency FGAs. This syndrome is manifested by agitation, confusion, changing levels of consciousness, muscle rigidity, fever, tachycardia, autonomic instability, and diaphoresis. The mortality rate is high and should be treated as a medical emergency. Discontinue the offending agent and give supportive therapy, including fluids and cooling. Bromocriptine and dantrolene have been used with varying success. Do not reinitiate antipsychotics until at least 14 days after resolution of NMS symptoms.
5. Hyperprolactinemia: Antipsychotics, particularly FGAs, can block the effects of dopamine in the tuberoinfundibular pathway. This increases prolactin excretion, which can lead to breast enlargement, galactorrhea, sexual dysfunction, infertility, and menstrual changes. Among the SGAs, risperidone and paliperidone may cause hyperprolactinemia. Because aripiprazole has partial dopaminergic agonist activities, it can lower prolactin concentrations.
6. Sexual dysfunction: Erectile dysfunction occurs in 23%–54% of men. Loss of libido and anorgasmia may occur in men and women.
7. Weight gain and diabetes: Weight gain occurs in up to 40% of patients. Diabetes can also develop, with 60% of cases occurring within the first 6 months. Among the SGAs, the risk is highest with clozapine and olanzapine, followed by quetiapine and risperidone. Among the FGAs, low-potency agents have a higher risk than high-potency agents. Important interventions include keeping the dose as low as possible and implementing dietary management to minimize weight gain. Weight gain may occur because of actions at histamine or serotonin receptors.
8. QTc prolongation: Electrocardiographic (ECG) changes occur with antipsychotics. QTc prolongation can predispose the patient to ventricular arrhythmias, including torsades de pointes. The risk of QTc prolongation appears highest with chlorpromazine, intravenous haloperidol, and thioridazine. Among the SGAs, clozapine, ziprasidone, and iloperidone appear to have the highest risk, though the other agents may cause ECG changes to a lesser extent or when combined with other agents that prolong the QTc interval. Patients must be assessed for predisposing factors such as preexisting ECG abnormalities, electrolyte disturbances, and concurrent therapy with other drugs that prolong the QTc interval. A list of medications that can prolong the QTc is available at https://www.crediblemeds.org/.
9. Seizures: Antipsychotic medications lower the seizure threshold. The risk is highest with predisposing factors. Chlorpromazine, cariprazine, and clozapine carry the highest risk. Aripiprazole, fluphenazine, haloperidol, pimozide, risperidone, thioridazine, and trifluoperazine carry the lowest risk.

10. Thermoregulation: Antipsychotics are associated with poikilothermia, or difficulty regulating the body temperature. Patients should use caution when exercising or during exposure to high temperatures because hyperthermia can occur. In addition, the anticholinergic effects of antipsychotics can interfere with sweating, further compounding the problem. Patients should be educated to avoid the heat and, if they cannot, to hydrate well. Hypothermia is a risk with low temperatures. Thermoregulatory problems are more common with low-potency FGAs, but they are also possible with SGAs having more anticholinergic properties, such as clozapine, olanzapine, and quetiapine.

G. Drug-Drug Interactions: Many antipsychotics are metabolized by the cytochrome P450 (CYP) system (Table 4). The presence of a CYP inducer or inhibitor may require antipsychotic dose adjustment. For example, tobacco dependence, particularly smoking, is common in patients with schizophrenia. A patient taking a CYP1A2 substrate antipsychotic who undergoes smoking cessation may require a reduced antipsychotic dose. This is particularly true of clozapine, olanzapine, and asenapine. Many SGAs metabolized by 2D6 and/or 3A4 carry dose adjustment recommendations.

Table 4. Selected Antipsychotics and the CYP System

	1A2	2D6	3A4
Substrate	Asenapine Clozapine[a] Olanzapine Ziprasidone	Aripiprazole Brexpiprazole[a] Iloperidone[a] Perphenazine Risperidone	Aripiprazole Brexpiprazole[a] Cariprazine[a] Haloperidol Iloperidone[a] Lumateperone[b] Lurasidone[a] Pimavanserin[a] Quetiapine[a] Ziprasidone
Inducer	Smoking tobacco		
Inhibitor		Chlorpromazine Fluphenazine	

[a]Dose adjustment required when used concomitantly with an inhibitor or inducer of that specific CYP enzyme.

[b]Avoid use with concomitant inducers or inhibitors.

H. FGAs for Schizophrenia: Administration Tips and Specific Agents
1. Oral tablet therapy is the most common.
2. Parenteral antipsychotics can be used acutely if patients do not adhere to therapy, are agitated and will not take oral medications, or are a danger to themselves and/or others. Several FGAs are available as parenteral injections that are given intramuscularly, including fluphenazine and chlorpromazine, but haloperidol is most commonly used. Intravenous haloperidol has been linked to cardiac toxicity, including torsades de pointes, and is not recommended.

3. Loxapine (Adasuve) is available in an inhalable formulation for the treatment of agitation associated with schizophrenia or type I bipolar disorder. Patients should be screened for pulmonary disease. Inhalable loxapine should not be administered to patients with a history of asthma, chronic obstructive pulmonary disease, or other forms of bronchospasm. Loxapine has a Risk Evaluation and Mitigation Strategies (REMS) program associated with the bronchospasm. Health professionals must be specially trained on the Adasuve system and have supplies on hand to treat bronchospasm, including a short-acting bronchodilator such as albuterol, a nebulizer, and nebulizer solution. The most common adverse effects include dysgeusia, sedation, and throat irritation.
4. Depot forms (or long-acting injectables [LAIs]) of haloperidol and fluphenazine are available, providing sustained concentrations for about 1 month for haloperidol and 2–3 weeks for fluphenazine. LAIs are indicated as chronic therapy in patients who have benefitted from and have tolerability to oral therapy, but may have difficulty adhering to taking a daily medication, or patient preference. Both haloperidol and fluphenazine decanoate may require "bridging" (oral overlap) with oral therapy when treatment is initiated. Haloperidol decanoate can alternatively be loaded without the need for overlap with oral medication.

I. SGAs for Schizophrenia: Specific Agents
   1. Clozapine (Clozaril): The first "atypical" antipsychotic. Clozapine is indicated only for treatment-resistant schizophrenia (defined as lack of response to two or more adequate trials of antipsychotics, usually of different classes). Lack of response usually refers to positive symptoms, though it may also include negative symptoms. Clozapine is also indicated in patients with schizophrenia or schizoaffective disorder who have suicidal ideation. The APA endorsees this indication as well as clozapine for patients with schizophrenia with substantial aggressive behavior despite other treatments. Clozapine is not associated with EPS or tardive dyskinesia, and it better reduces negative symptoms than FGAs.
      a. Several black box warnings limit its use.
         i. Severe neutropenia (agranulocytosis): This is the most limiting adverse effect. Severe neutropenia can lead to a dramatic decrease in neutrophils, which increases the risk of serious or fatal infections. Severe neutropenia is defined as an absolute neutrophil count (ANC) less than 500 cells/mm^3. The incidence is about 0.9% and is highest during the first 4–6 months of therapy. Previously, both the white blood cell count and the ANC were used to monitor safety. As of 2015, only the ANC is used, and lower values are allowed for therapy. Allowances are also made for patients who have benign ethnic neutropenia (included in Table 5). Because of the severity of the neutropenia, all patients must be registered under a centrally managed REMS program (www.clozapinerems.com), which consolidates the six previous individual programs. Prescribers and pharmacies must also be registered. Laboratory work must be submitted to the national registry before clozapine can be dispensed. Table 5 presents details of hematologic monitoring.

Table 5. Hematologic Monitoring for Clozapine

ANC Concentration	Clozapine Treatment Recommendations	ANC Monitoring
Normal range for a new patient: General population (> 1500 cells/mm^3) BEN population (≥ 1000 cells/mm^3) Obtain at least two baseline ANC concentrations before initiating treatment	Initiate treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient	Weekly from initiation to 6 mo Every 2 wk from 6 to 12 mo Monthly after 12 mo
Mild neutropenia (1000–1499 cells/mm^3)[a]	GENERAL POPULATION Continue treatment	GENERAL POPULATION Three times weekly until ANC ≥ 1500 cells/mm^3 Once ANC ≥ 1500 cells/mm^3, return to patient's last "normal-range" ANC monitoring interval
	BEN POPULATION Mild neutropenia is normal range for BEN population, continue treatment Obtain at least two baseline ANC concentrations before initiating treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia	BEN POPULATION Weekly from initiation to 6 mo Every 2 wk from 6 to 12 mo Monthly after 12 mo
Severe neutropenia (< 500 cells/mm^3)[a]	GENERAL POPULATION Recommend hematology consult Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines that benefits outweigh risks	GENERAL POPULATION Daily until ANC ≥ 1000 cells/mm^3 Three times weekly until ANC ≥ 1500 cells/mm^3 If patient rechallenged, resume treatment as a new patient under "normal-range" monitoring once ANC ≥ 1500 cells/mm^3
	BEN POPULATION Recommend hematology consult Interrupt treatment for suspected clozapine-induced neutropenia Do not rechallenge unless prescriber determines that benefits outweigh risks	BEN POPULATION Daily until ANC ≥ 500 cells/mm^3 Three times weekly until ANC ≥ a patient's established baseline If patient rechallenged, resume treatment as a new patient under "normal-range" monitoring once ANC ≥ 1000/mm^3 or at patient's baseline

[a]Confirm all initial reports of ANC > 1500 cells/mm^3 with a repeat ANC measurement within 24 hr.

[b]If clinically appropriate.

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia.

Information from: Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers. Available at https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/ANC_Table.pdf. Accessed November 14, 2020.

(a) OH, bradycardia, syncope, and cardiac arrest: Are dose related and patients are at highest risk at initiation of therapy or with rapid dose titration. Must be initiated at 12.5 mg once or twice daily, titrated slowly, and given in divided doses
(b) Seizures: Risk is dose related and can be minimized by starting low and titrating slowly.
(c) Myocarditis and cardiomyopathy: These are rare. They can occur at any point in treatment; however, myocarditis is more common in the first 2 months of treatment, and cardiomyopathy is more common after 8 weeks of treatment. Cardiomyopathy is usually delayed in onset. Risk factors for myocarditis include rapid dose titration and initiation of clozapine at high doses. If patients develop either of these, they should not be rechallenged with clozapine unless benefits are judged to outweigh risks.

ii. Additional adverse effects include weight gain, sedation, hypersalivation, rapid heart rate, anticholinergic adverse effects, and fever. The presence of fever should alert the clinician to the possibility of infection and agranulocytosis. If the drug is discontinued for 48 hours or more, retitration is required to avoid seizures or cardiac adverse effects.
iii. In January 2020, the FDA strengthened an existing warning regarding clozapine-associated constipation. It can progress to serious complications, including necrotizing colitis and intestinal ischemia, hospitalization, and death. Risk increases with clozapine dose and when clozapine is combined with other medications that can slow GI motility.

b. Aripiprazole (Abilify):
i. Aripiprazole is a partial agonist at D_2 with high affinity for the D_3 receptor. As a result, it is not associated with hyperprolactinemia.
ii. Has a low risk of most forms of EPS, including tardive dyskinesia. Is associated with a high incidence of akathisia
iii. Aripiprazole has been associated with pathological gambling and other compulsive behaviors, which may be related to its affinity for D_3.
iv. Available in two LAIs: Abilify Maintena and aripiprazole lauroxil [Aristada]. As with any other LAIs, patients should demonstrate tolerability with the oral formulation before receiving the injection. Abilify Maintena requires 14 days of overlap with oral aripiprazole. Aristada Initio is a special formulation of aripiprazole lauroxil that is intended to be given as a single 675-mg dose with 30 mg of oral aripiprazole to initiate long-acting aripiprazole lauroxil or reinitiate therapy after a missed dose of aripiprazole lauroxil. This formulation is not intended to be used as a repeat injection. If Aristada is initiated without the Initio formulation, a 21-day overlap with oral aripiprazole is required.
v. Aripiprazole is also available as a tablet that contains an ingestible event marker that detects when the medication has been taken and is tracked through a smartphone app and web portal (Abilify MyCite).

c. Asenapine (Saphris) is available only as a sublingual formulation and as a patch (Secuado).
i. It is important to avoid eating or drinking for 10 minutes after administration of the sublingual tablet.
ii. The patch is changed daily. It can be worn while showering but has not been evaluated for bathing or swimming.
iii. Asenapine has been associated with a high risk of orthostasis and sedation.
iv. There has also been a warning about the risk of hypersensitivity reactions with asenapine.
v. Asenapine use is contraindicated in severe hepatic impairment (Child-Pugh class C).

d. Brexpiprazole (Rexulti):
i. Chemically related to aripiprazole
ii. The most common dose-dependent adverse effects are akathisia, weight gain, and somnolence. Clinically significant weight gain (greater than 7%) occurs in 8%–12% of patients. Brexpiprazole can also cause hyperglycemia and dyslipidemia.

iii. Must be adjusted for renal function (CrCl less than 60 mL/minute/1.73 m^2) and moderate to severe hepatic impairment (Child-Pugh class B or C)
iv. Like aripiprazole, brexpiprazole may increase the risk of pathological gambling and other compulsive behaviors.

e. Cariprazine (Vraylar):
i. Cariprazine has a half-life of 2–4 days. It also has active metabolites that have long half-lives (DCAR 1–2 days, DDCAR 1–3 weeks). Hence, changes in dose may not be reflected clinically for long periods.
ii. Cariprazine is not recommended for patients with a CrCl of less than 30 mL/minute/1.73 m^2 or severe hepatic impairment (Child-Pugh class C).
iii. Cariprazine is associated with dose-related OH, particularly at initiation and with dose increases.
iv. Limited studies suggest a low rate of weight gain over 6 weeks (1%–8% incidence, with 8% of those gaining more than 7%). Other adverse drug reactions include gastrointestinal (GI) symptoms, somnolence, dizziness, parkinsonism (13%–21%), and seizures.
v. Leukopenia and neutropenia have occurred, but there are no current recommendations to monitor.

f. Iloperidone (Fanapt)
i. Iloperidone has a high risk of orthostasis but a lower risk of EPS, anticholinergic symptoms, and sedation. Iloperidone has a strict titration schedule to minimize OH.
ii. Short- and long-term studies have also shown an association with QTc prolongation similar to that of haloperidol and ziprasidone.
iii. Dosage should be adjusted for moderate intensity, and use should be avoided in severe hepatic impairment.

g. Lumateperone (Caplyta)
i. Approved in December 2019 for the treatment of schizophrenia
ii. Has presynaptic partial agonism and postsynaptic antagonism for D_2 receptors and at least 60 times more affinity for the serotonin-2A receptor than the D_2 receptor. This is theorized to be associated with the low incidence of EPS in clinical trials. It also indirectly modulates glutamatergic activity.
iii. The recommended starting and target doses are both 42 mg daily. It should be administered with food.
iv. The most common adverse effects are sedation/somnolence, dry mouth, fatigue, nausea, constipation, and dizziness.
v. Avoid use with CYP3A4 inducers or inhibitors. It is also a substrate for UGT (UDP glucuronosyltransferase).
vi. Avoid use in moderate and severe hepatic impairment (Child-Pugh class B or C).

h. Lurasidone (Latuda)
i. Has a low risk of metabolic and cardiac effects
ii. Dose-related EPS may occur.
iii. Lurasidone should be taken with at least 350 kcal of food.
iv. The dose must be tapered for moderate and severe renal impairment, when used with a moderate CYP3A4 inhibitor (e.g., diltiazem), and for moderate and severe hepatic impairment.

i. Olanzapine (Zyprexa):
i. This drug is structurally similar to clozapine and has a similar pharmacologic profile.
ii. Unlike clozapine, it does not require strict monitoring for agranulocytosis.
iii. In one study, negative symptoms responded better to olanzapine than to haloperidol.
iv. Together with clozapine, olanzapine carries the highest risk of diabetes. For this reason, many schizophrenia treatment guidelines do not consider it first-line therapy.

v. Olanzapine is also available as a depot injection olanzapine pamoate (Zyprexa Relprevv). Because administration of olanzapine pamoate has been associated with extreme sedation and delirium, it is part of a REMS program (called the Zyprexa Relprevv Patient Care Program). Prescribers must undergo training, and it can only be administered within an approved institution where the patient has postdose supervision for 3 hours.

j. Paliperidone (Invega)
   i. The major active metabolite of risperidone. Paliperidone's pharmacologic profile is similar to that of the parent drug (see the text that follows).
   ii. Paliperidone palmitate is also available as an LAI in both monthly (Invega Sustenna) and 3-month (Invega Trinza) formulations. As with other LAI formulations, oral tolerability should be established before changing to the LAI. No overlap with oral medication is needed for either LAI formulation.
   iii. Adjustment for renal function is required.

k. Pimavanserin (Nuplazid)
   i. Currently indicated only for psychosis associated with Parkinson disease, but is being studied as an adjunctive treatment for patients with schizophrenia who have predominantly negative symptoms
   ii. Lacks affinity for D_2 receptors. Is an inverse agonist at serotonin-2C receptors. Although classified as an SGA, it is structurally different from any other member of this class.
   iii. Has a large volume of distribution and a long half-life (55–60 hours), with an active metabolite with a half-life of 200 hours
   iv. The most common adverse effects include headache, dizziness, nausea, peripheral edema, and confusion.
   v. The dose is 34 mg once daily. It is metabolized by CYP3A4. The dose must be tapered when given with a strong 3A4 inhibitor. Pimavanserin should be avoided with strong CYP3A4 inducers.

l. Quetiapine (Seroquel):
   i. In addition to antagonism at the D_2 and serotonin-2C receptors, quetiapine has a high affinity for histamine-1 receptors. Therefore, quetiapine has a high incidence of somnolence and weight gain. May also cause OH
   ii. Unlike other antipsychotics, quetiapine has a low incidence of EPS. Hence, quetiapine is often used for psychosis associated with Parkinson disease, despite the lack of strong evidence for efficacy.

m. Risperidone (Risperdal):
   i. This drug is a potent dopamine D_2 antagonist and a serotonin-2C antagonist with limited anticholinergic activity.
   ii. At doses of up to 6 mg/day, the incidence of EPS has been no higher than with placebo in clinical studies. However, EPS is a dose-related phenomenon that may occur in patients taking the drug even at usual doses.
   iii. Patients often tolerate risperidone better than haloperidol. However, this increase in tolerability compared with haloperidol is lost at high doses of risperidone.
   iv. Adverse effects include sedation, OH, weight gain, sexual dysfunction, and hyperprolactinemia.
   v. Dose must be tapered for CrCl less than 30 mL/minute/1.73 m^2 and severe hepatic impairment (Child-Pugh class C).
   vi. A long-acting intramuscular formulation (Risperdal Consta) is available. This formulation is administered every 2 weeks and requires a 3-week bridge therapy with oral risperidone.
   vii. Risperidone is also now available as a monthly LAI that is administered subcutaneously (Perseris). This injection does not require oral overlap.
   viii. Like with other LAIs, tolerability with oral therapy should be established before initiating either of the long-acting formulations of risperidone.

n. Ziprasidone (Geodon):
   i. Has a low incidence of metabolic syndrome, but can prolong the QTc interval. Use caution if combining it with other drugs (e.g., tricyclic antidepressants [TCAs] or antiarrhythmics) that can also increase the QTc interval.
   ii. Ziprasidone is also available in a parenteral formulation for acute agitation.
   iii. Ziprasidone must be taken with food (at least 500 kcal) to increase absorption.
   iv. Ziprasidone carries a warning for drug reaction with eosinophilia and systemic symptoms (DRESS), which can be fatal. It consists of three or more cutaneous reactions (including rash or exfoliative dermatitis), eosinophilia, fever, and lymphadenopathy and one or more of the following systemic complications: hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.

J. Treatment Goals
   1. Acute
      a. Reduce acute symptoms.
      b. Return patient to baseline level of function.
   2. Maintenance
      a. Prevent recurrence of symptoms.
      b. Maximize functioning and quality of life.

K. Nonpharmacologic Treatment of Schizophrenia
   1. A comprehensive, person-centered treatment plan should be developed and documented. Elements should include treatment setting, plans for addressing risks of harm to self or others, barriers to adherence, and goals of treatment.
   2. Psychosocial interventions that benefit patients include cognitive behavioral therapy (CBT) for psychosis, psychoeducation, supported employment services, cognitive remediation, social skills training, and supportive psychotherapy.
   3. Patients with schizophrenia with a history of poor engagement with services that lead to frequent relapse or social disruption, such as homelessness and legal difficulties including imprisonment, should be offered assertive community treatment.
   4. Patients with schizophrenia should receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.
   5. When assessing adherence, a patient-centered approach is crucial, particularly if anosognosia exists. Methods that enhance the therapeutic alliance, such as motivational interviewing, and that are objective and nonjudgmental have the greatest chance of success.

L. Treatment with Antipsychotics
   1. Choosing an antipsychotic: In practice, SGAs are preferred as first-line treatment. However, most guidelines recommend either an FGA or an SGA. The 2020 APA guidelines recommend individualizing treatment to the specific patient. This includes gathering information on previous treatment experiences and responses and the patient's treatment preferences and discussing the potential risk-benefit of potential medications, as well as other treatment options.
   2. Therapy initiation
      a. First episode: Younger or treatment-naive patients may be more sensitive to adverse effects and may respond more quickly to treatment. Hence, it is recommended to start with a lower dose. This may also improve chances of adherence by avoiding adverse effects.
      b. In patients with a history of treatment with antipsychotics, higher doses and more aggressive titrations may be appropriate.

   c. Older individuals with concomitant physical health issues and medications may need starting doses that are as small as one-fourth to one-half the usual adult starting dose.
   d. Once medication is initiated, escalation to a therapeutic dose can be achieved relatively rapidly, though this will vary depending on the individual drug.
3. Dose optimization:
   a. Can be difficult to determine during the acute phase because it may take patients 2–4 weeks to show an initial response with conservative titration; often, more aggressive titration is used for inpatients to hasten response. This must be weighed against the increased risk of adverse effects. It may take longer to show optimal response.
   b. Data suggest that patients who have experienced less than a 20% response after 2 weeks on a therapeutic dose are unlikely to be much improved at 4–6 weeks (as reflected by a 50% or greater reduction in symptoms). Thus, response should be assessed at 2–4 weeks after achieving a therapeutic dose.
   c. Patients should continue to be treated with the same medication that improved their symptoms.
4. Therapy duration: The chronicity of schizophrenia usually results in lifelong antipsychotic treatment. Benefits of a particular medication must be weighed against long-term adverse effects (e.g., tardive dyskinesia) when selecting a specific antipsychotic. Relapse rates within the first year of medication discontinuation are greater than 50%; thus, maintaining the antipsychotic at the minimal effective dose continuously may be the best approach for most patients. Long-term therapy should include monitoring for metabolic complications such as diabetes, weight gain, and lipid abnormalities, as well as abnormal movements.
5. Treatment-resistant schizophrenia: Clozapine is the agent of choice. See the Clozapine section earlier for more details.
6. Use of several antipsychotics: Current data do not support routine combination of antipsychotics. Some data suggest benefit for augmenting clozapine, but more information is needed.

M. Adjunctive Medications
1. Lamotrigine may be beneficial when added to clozapine in patients with partial response. Data do not support the use of other anticonvulsants, including valproate, carbamazepine, and topiramate.
2. Benzodiazepines: May be useful during the acute phase for agitation or anxiety but are less effective for psychotic symptoms. These drugs must also be used with caution in patients with schizophrenia because this population is at high risk of substance use disorder (SUD).
3. Antidepressants are indicated when patients with schizophrenia develop depression.

Patient Case

Questions 5–8 pertain to the following case.

A 45-year-old woman has a medical history significant for sleep apnea, hypertension, type 2 diabetes, chronic pain, and bulimia. She is in the clinic today for an assessment of her depressive symptoms and a medication evaluation. She endorses sad mood, poor appetite (lost 6.8 kg [15 lb]), poor concentration, and feelings of hopelessness and worthlessness for the past 3 weeks. She has also stopped going to her book club because she is not motivated to get out of the house, and she has frequent nocturnal awakening. She denies suicidal or homicidal ideation. She denies any use of alcohol, tobacco, or illicit drugs. She currently takes hydrochlorothiazide, metformin, hydrocodone/acetaminophen, and aspirin. Her current BMI is 20 kg/m^2, and her blood pressure today is 152/94 mm Hg. She reports adherence to her current medications.

1. Which selective serotonin reuptake inhibitor (SSRI) would most likely interact with her current medications?
   A. Citalopram.
   B. Fluvoxamine.
   C. Paroxetine.
   D. Sertraline.

2. Which antidepressant would be most appropriate for her depressive symptoms?
   A. Bupropion.
   B. Fluoxetine.
   C. Mirtazapine.
   D. Venlafaxine.

3. It has been 4 weeks since her initial visit with you, and she has been treated with citalopram 20 mg/day in the morning. She still presents with sad mood, but her insomnia, concentration, and appetite have improved. However, she still has feelings of hopelessness and worthlessness, lack of motivation, and anhedonia. She has no adverse effects. At this point, which is the best recommendation to optimize her therapy?
   A. Continue at current dose of 20 mg/day.
   B. Increase the current dose to 40 mg/day.
   C. Add aripiprazole.
   D. Change to a different SSRI.

4. Six months later, she reports that although her depression symptoms have resolved, she has "trouble" during intercourse, which is quite disturbing to her. You determine that she has anorgasmia caused by citalopram treatment. Which is the most appropriate recommendation at this time?
   A. Discontinue citalopram.
   B. Add bupropion to citalopram.
   C. Change to a different SSRI.
   D. Change to vortioxetine.

II. MAJOR DEPRESSIVE DISORDER (MDD)

A. Identification of Depressive Disorders. This overview is based on the *DSM-5*; please consult for complete diagnostic criteria.
   1. MDD is also called unipolar depression, or just depression. MDD is diagnosed when a patient has at least five of the following symptoms almost every day for at least 2 weeks:
      a. Must have a depressed mood or anhedonia (loss of interest in pleasurable activities)
      b. Additional symptoms include sleep disturbances, changes in weight or appetite, decreased energy, feelings of guilt or worthlessness, psychomotor retardation or agitation, decreased concentration, and suicidal ideation.
      c. The symptoms must interfere with the patient's everyday ability to function.
   2. Persistent depressive disorder (dysthymia): Chronic depressed mood occurring more days than not for at least 2 years but that does not meet the criteria for MDD.

B. Assessment of Patients with MDD
   1. Psychiatric history: A thorough history of symptoms is compared with the diagnostic criteria, and the diagnosis is made from the collected data.
   2. Clinician rating scales: Psychometric instruments used to identify depression and assess its severity. Common examples include:
      a. Hamilton Rating Scale for Depression (HAM-D): Often used to show efficacy in clinical trials for FDA approval of antidepressants. A common clinical trial enrollment score is greater than 18 (moderate-severe depression). A response is usually defined as at least a 50% reduction in the HAM-D score. "Remission" is a return to a normal state or a HAM-D of 7 or less.
      b. CGI (Clinical Global Impressions) scale is a clinician-rated scale that evaluates the severity and improvement of patients overall.
      c. MADRS (Montgomery-Åsberg Depression Rating Scale) also evaluates symptoms of depression. It is commonly used in clinical trials.
   3. Patient rating scales: Patient-completed rating instruments. Answers to the questions are used to identify and assess the level of depression.
      a. Patient Health Questionnaire-9 (PHQ-9) is based on the *DSM-5* diagnostic criteria for major depression. The PHQ-9 is easily administered and assessed. For this reason, it is often used in the primary care setting. Patients can be screened with an abbreviated version (the PHQ-2). If patients test positive, the PHQ-9 is administered. The PHQ-9 can also be used to monitor treatment response.
      b. Beck Depression Inventory
      c. Quick Inventory of Depressive Symptoms: Self-Rated
      d. Geriatric Depression Scale (GDS)
   4. Physical examination and laboratory tests: Necessary to rule out physical causes (e.g., thyroid disorders, vitamin deficiencies) that may mimic symptoms of depression
   5. Biologic testing: Depression is commonly associated with abnormalities in the dexamethasone suppression test and tests of the thyroid axis. However, these tests are not routinely used in clinical practice.
   6. Medications and substances (e.g., interferons, benzodiazepines, barbiturates, alcohol, central nervous system [CNS] depressants, withdrawal from stimulants, cocaine, amphetamines) can have depression as an adverse effect. Pharmacists should perform a medication and substance use review to identify possible causes.
   7. All patients should be screened for suicidal ideation.
      a. The National Suicide Hotline is 1-800-273-8255 (TALK).
      b. The website is https://suicidepreventionlifeline.org/.
      c. On July 16, 2020, the FCC adopted rules to establish 988 as the new 3-digit phone number to connect Americans with suicide prevention and mental health counselors. All 988 calls will connect with the National Suicide Hotline by July 16, 2022.

C. Therapeutic Options
   1. Nonpharmacologic treatment options: Examples include interpersonal psychotherapy and CBT. It takes longer to achieve effective results with psychotherapy than with pharmacotherapy. Psychotherapy may have broader and longer-lasting effects than pharmacotherapy monotherapy. Psychotherapy is recommended as monotherapy for initial treatment in patients with mild to moderate MDD (CBT and interpersonal therapy have the best evidence). Psychotherapy combined with pharmacotherapy is recommended for moderate to severe depression. Combination is more effective than either intervention alone.
   2. Pharmacotherapy: Antidepressant therapy may lead to a more rapid response than psychotherapy, but when discontinued, there is a risk of relapse and adverse effects.
   3. Electroconvulsive therapy (ECT): Option for refractory depression, depression in pregnancy, psychotic depression, and other conditions for which medications may not be optimal or effective. The usual induction cycle is two or three treatments per week for 6–12 treatments. Maintenance dosing is individualized to the patient, and frequency can vary from weekly to monthly. Temporary memory loss is common, and medications that affect seizure threshold must be tapered before treatment. ECT is also suggested as initial treatment if symptoms are severe or life threatening.

D. Pharmacotherapeutic Options: Considerations and Keys to Use
   1. Selection: All antidepressants are considered equally efficacious. First-line medications include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, and vortioxetine. Consider possible drug-drug and drug-disease interactions, concurrent illnesses, prior responses, family members' prior responses, patient preference, and cost.
   2. Adequate trial: An adequate trial includes the correct drug for the patient and a therapeutic dose for an appropriate duration. A therapeutic trial lasts 4–8 weeks.
   3. Response and remission: A response is usually defined as a 50% reduction in symptoms. Remission is a return to normal mood (e.g., HAM-D of 7 or less; PHQ-9 less than 5). Remission is also defined as at least 3 weeks with no symptoms of depressed mood and anhedonia and no more than three remaining symptoms of depression. Remission is the goal of therapy. Optimizing the dose or duration is important for achieving remission.
   4. Treatment phases
      a. Acute
         i. The goal of this phase is remission.
         ii. Onset of antidepressant effect: Physical symptoms (energy levels, sleep disturbances) improve before affective symptoms. For this reason, patients with suicidal ideation may be at an increased risk of carrying out plans during this phase and should be closely monitored. Early response (20%–30% reduction in symptoms) in the first 2–4 weeks is a strong predictor of remission at 12 weeks. A patient who has a partial response in the first 4 weeks should be allowed a longer trial (and at the full therapeutic dose) before moving on to other therapy. In general, it takes 4–6 weeks to see the full effect of antidepressants, given the correct drug, dose, and adherence, but it may take as long as 8 weeks to see a response. Remission may take up to 12 weeks.
         iii. Monitoring therapy: Patients should be monitored for response through interviews or by repeating rating scales. In addition, patients (and their support systems, if available) should be educated about therapy and closely monitored for adverse effects. Although most of the adverse effects are not life threatening, they do affect adherence.
         iv. Nonresponders: A nonresponder can be changed to another antidepressant within either the same class or a different class. A patient who does not respond to one SSRI may respond to another in the same class, as shown in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

b. Maintenance
    i. Once a patient has achieved remission, treatment should continue for at least another 6–9 months.
    ii. Those with risk factors for recurrent depression should receive treatment for 2 years or longer. Risk factors include frequent, recurrent episodes; severe episodes (including psychosis, severe impairment, or suicidality); chronic episodes; presence of comorbid psychiatric or medical conditions; and presence of residual symptoms or difficult-to-treat episodes.

5. Efficacy of antidepressants according to rigorous clinical trials occurs in 60%–70% of patients, regardless of drug. Effectiveness, which is more reflective of clinical practice, is lower, about 50%–60%. The remission rate with one antidepressant trial is about 30%, as seen in the STAR*D trial.
6. Drug interactions (Table 6): Many antidepressants are metabolized or inhibited by CYP enzymes. (Hereafter, CYP enzymes will only be referred to by pathway [e.g., 1A2, 2D6, 3A4].)

Table 6. Antidepressants and the CYP System[a]

	1A2	2C19	2D6	3A4
Substrate	Duloxetine	Citalopram Escitalopram Fluoxetine Imipramine Vilazodone	Amitriptyline Desipramine Duloxetine Fluoxetine Imipramine Nefazodone Nortriptyline Trazodone Venlafaxine Vortioxetine	Citalopram Escitalopram Levomilnacipran Nefazodone Trazodone Venlafaxine Vilazodone
Inducer	Smoking tobacco	St. John's wort		St. John's wort
Inhibitor	**Fluvoxamine**	Amitriptyline Fluoxetine Fluvoxamine Imipramine	**Bupropion**[b] Duloxetine Fluoxetine Paroxetine Sertraline	Fluvoxamine **Nefazodone**

[a]Boldface type in table body indicates strong inhibitor.

[b]Metabolized by CYP2B6.

E. Selective Serotonin Reuptake Inhibitors (Table 7)
    1. SSRIs selectively inhibit the reuptake of serotonin into the presynaptic neuron and desensitize the presynaptic serotonin autoreceptor, resulting in increased serotonin concentrations. Two additional SSRIs, vortioxetine and vilazodone, have additional activity and are covered separately in the text that follows.

Table 7. SSRI Characteristics

Characteristic	Citalopram (Celexa)	Escitalopram (Lexapro)	Fluoxetine (Prozac)	Fluvoxamine[a] (Luvox)	Paroxetine (Paxil)	Sertraline (Zoloft)
Half-life	32 hr	27–32 hr	1–4 days	15 hr	21 hr	26 hr
Active metabolite	No	No	Yes[b]	No	No	No
Usual dose (mg/day)	20–40	10–20	20–60	50–300	10–60	50–200
Maximum daily dose (mg)	40	20	80	300	50 (depression) 60 (anxiety)	200

[a]Indicated only for obsessive-compulsive disorder; seldom used for depression.

[b]Norfluoxetine.

2. The efficacy of SSRIs is equal for the treatment of depression. Adverse effect profiles differ slightly, and patients may tolerate one SSRI better than another.
3. Blockade of serotonin reuptake leads to an increase in serotonin overall and may influence all subtypes of serotonin receptors. Some (serotonin-2A, -2C, -3, and -4) may be responsible for some of the unwanted adverse effects (e.g., insomnia, restlessness, GI concerns). Activation, agitation, anxiety, or panic may occur in some patients, especially during the early phase of therapy. The most common adverse effects associated with this class of agents include GI concerns, insomnia, restlessness, headache, and sexual dysfunction. In general, the most activating SSRIs are fluoxetine and sertraline, whereas paroxetine and fluvoxamine are the most sedating. Citalopram and escitalopram have no appreciable sedating or activating effects. Sexual dysfunction is more common than reported in the prescribing information and may occur in 50% or more of patients receiving these agents. Interventions to consider for SSRI-induced sexual dysfunction in both sexes include using the wait-and-see method, adding bupropion for the treatment of sexual dysfunction, and lowering the SSRI dose. PDE-5 (phosphodiesterase type 5) inhibitors may be beneficial for men with erectile dysfunction. Data are less robust for women. Other interventions with weaker data include buspirone and mirtazapine.
4. Because these drugs have such potent serotonergic activity, combinations with other drugs affecting serotonin can lead to serotonin syndrome. Examples include the monoamine oxidase inhibitors (MAOIs), dextromethorphan, meperidine, sympathomimetics, linezolid, lithium, TCAs, and SNRIs. Although triptans have traditionally been listed among the agents to watch, a 2010 statement released by the American Headache Society reports poor evidence for the interaction. The finding was supported by a 2018 article (JAMA Neurol 2018;75:566-72) suggesting that the FDA reconsider the advisory. Triptans bind to different serotonin receptors than SSRIs or SNRIs and thus pose a low risk. Serotonin syndrome includes symptoms from three clusters: neuromuscular hyperactivity (e.g., myoclonus, rigidity, tremors, incoordination), altered mental status (agitation, confusion, hypomania), and autonomic instability (hyperthermia, diaphoresis). Serotonin syndrome can be subtle in onset or confused with NMS. Several criteria exist to identify serotonin syndrome, with the Hunter criteria considered the most accurate. These rely heavily on neurologic findings, with the presence of clonus being the most prominent, though tremor plus hyperreflexia are also considered adequate for diagnosis. Treatment includes discontinuing the offending agent, providing supportive measures such as cooling blankets and respiratory assistance, and providing a benzodiazepine for myoclonus, anticonvulsants for seizures, and nifedipine for hypertension.
5. SSRIs have been associated with EPS, including akathisia, dystonia, and bradykinesia, but these are uncommon. EPS appear to result from an effect of serotonin on dopaminergic neurotransmission in the basal ganglia.

6. SSRIs can cause hyponatremia of the SIADH (syndrome of inappropriate antidiuretic hormone secretion) type, particularly in older adult patients. Individuals should be monitored for symptoms suggestive of hyponatremia.
7. A withdrawal syndrome has been observed, especially for the drugs with shorter half-lives, so a gradual dose reduction (e.g., over 2–4 weeks) may be indicated. Symptoms include flu-like symptoms, such as nausea and chills, and neurologic symptoms, such as paresthesias, insomnia, anxiety, and "electric shock"–type sensations. If the problem is severe or persists, the SSRI can be reinitiated and the dose gradually reduced again. The timing of withdrawal syndrome symptoms correlates with SSRI half-life, so withdrawal symptoms occur the earliest with paroxetine. Even though fluoxetine has a significantly longer half-life, withdrawal symptoms may still occur and be delayed in onset.
8. The FDA ordered changes to citalopram package labeling, limiting the daily dose to no more than 40 mg because of an increased risk of QTc prolongation at daily doses greater than 40 mg. Patients who have risk factors for QTc prolongation (congenital long QTc syndrome, bradycardia, hypokalemia, hypomagnesemia, recent acute myocardial infarction, and uncompensated heart failure) or who are taking concomitant medications that may increase the QTc interval should not be treated with citalopram. The maximum recommended citalopram dose is 20 mg/day for patients with hepatic impairment, patients who are older than 60, patients who are 2C19 poor metabolizers, or patients who are taking concomitant 2C19 inhibitors.
9. These drugs are not as lethal in overdose cases as TCAs. All SSRIs listed in Table 7 are available in generic form. The low cost and better tolerability and safety of SSRIs warrant their use as first-line treatment of MDD in most patients.
10. Extended-dosing formulations: Fluoxetine 90 mg can be taken once weekly. Fluoxetine 90 mg is taken only during continuation therapy rather than as initial treatment. It is not commonly used in clinical practice. Paroxetine controlled release (CR) may have lower rates of nausea in the first week of treatment; efficacy is comparable, and both formulations are administered once daily. The weekly and CR products are available in generic form but are higher in cost.
11. Escitalopram is the *S*-isomer of citalopram and is the active component of the racemic mixture. At a 10-mg dose, escitalopram is at least as effective as citalopram 20 mg, but at this dose, there are fewer adverse effects. At higher doses, this advantage is not as pronounced.
12. SSRIs appear to modestly increase the risk of bleeding by inhibiting the serotonin reuptake into platelets. This leads to a decrease in serotonin-mediated platelet activation. Case-control and cohort studies also suggest an increased incidence of both vertebral and non-vertebral bone fractures.

F. Serotonin-Norepinephrine Reuptake Inhibitors (Table 8)

Table 8. SNRI Characteristics

Characteristic	Desvenlafaxine (Pristiq)	Duloxetine (Cymbalta)	Levomilnacipran (Fetzima)	Venlafaxine (Effexor)
Half-life	10–11 hr	8–17 hr	21–29 hr	5–11 hr
Active metabolite	No	No	No	Yes
Usual dose (mg/day)	50	60	40–120	75–225
Maximum daily dose (mg)	100[a]	120[b]	120	225

[a]Doses > 50 mg do not necessarily confer further benefit.

[b]Doses of ~60 mg do not necessarily confer further benefit.

1. Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran block the reuptake of norepinephrine and serotonin. Although milnacipran is considered an SNRI, it is only FDA approved for fibromyalgia. Unlike TCAs, SNRIs have negligible effects at other receptors that cause anticholinergic or antihistaminic adverse effects, with the possible exception of duloxetine, which appears to have a slightly higher incidence of anticholinergic symptoms. Venlafaxine has a dose-related effect on norepinephrine compared with desvenlafaxine and duloxetine. At doses of less than 150 mg/day, venlafaxine is a serotonin reuptake inhibitor.
    a. Whether the dual action of venlafaxine makes it more effective than SSRIs is an area of continued research. Some patients (e.g., treatment nonresponders) appear to benefit either from agents that affect norepinephrine and serotonin or from combinations of drugs with that effect.
    b. The adverse effect profile of venlafaxine is similar to that of the SSRIs, with GI concerns being common. Of note, SNRIs can cause increases in blood pressure, which are usually mild and not clinically significant unless the patient has uncontrolled hypertension. This is a dose-related phenomenon, as described earlier, particularly for venlafaxine and desvenlafaxine. Levomilnacipran and desvenlafaxine are also associated with OH.
2. Levomilnacipran is the more potent enantiomer of milnacipran. Levomilnacipran is only approved for depression, not fibromyalgia. The dose must be adjusted in renal insufficiency, and the drug is not recommended in end-stage renal disease. Levomilnacipran can cause hyponatremia and increase bleeding risk. The capsule should not be crushed or opened. Levomilnacipran is metabolized through 3A4 (major pathway) and 2C19 and 2D6, among others (minor pathways). Monitor signs and symptoms of potential toxicities if 3A4 inhibitors are used concomitantly. Both blood pressure elevations and OH can occur. Levomilnacipran can cause an elevated heart rate and palpitations, which are common reasons for discontinuation. Levomilnacipran is a more potent inhibitor of norepinephrine than venlafaxine or duloxetine (norepinephrine is slightly preferred to serotonin).
3. All SNRIs can produce serotonin syndrome. In overdose situations, both duloxetine and venlafaxine have been associated with higher rates of death than SSRIs. The risk of death because of overdose of SNRIs is still lower than with TCAs.
4. Duloxetine has also been approved for the treatment of diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain caused by chronic lower back pain or osteoarthritis pain. Be careful when using this drug with 2D6 inhibitors. Monitor blood pressure because increases have been observed. Duloxetine can cause liver toxicity and should not be used in patients with hepatic insufficiency, end-stage renal disease requiring dialysis, or severe renal impairment.
5. SNRIs can cause a withdrawal syndrome similar to the SSRIs and thus should be tapered slowly when discontinued.

6. Desvenlafaxine is an active metabolite of venlafaxine. Benefits over the parent drug are limited. Because it bypasses CYP metabolism, it may be advantageous in patients with hepatic insufficiency or those taking major 2D6 inducers or inhibitors.
7. Renal dosing is required for both desvenlafaxine and levomilnacipran doses, and doses must be reduced with decreased renal function.

G. Mixed Serotonergic Medications
   1. Vilazodone (Viibryd) is an SSRI with partial agonist at the serotonin-1A receptor. The clinical significance of this effect is unknown. Vilazodone has a half-life of 25 hours but does not have active metabolites. Both the usual and maximum doses are 40 mg daily. Vilazodone should be taken with food. The most common adverse effects are nausea and diarrhea. Vilazodone may cause a lower incidence of sexual dysfunction. Vilazodone should not be used in patients with a history of seizure disorder. The dose must be decreased when given with strong 3A4 inhibitors. Postmarketing reports include acute pancreatitis and sleep paralysis, but the true frequency is unknown, and the FDA labeling has not been changed.
   2. Vortioxetine (Trintellix) is an SSRI, but its pharmacologic profile differs from other SSRIs. Vortioxetine has additional agonist activity at the serotonin-1A receptor, partial agonist activity at the serotonin-1B receptor, and antagonistic activity at the serotonin-3, serotonin-1D, and serotonin-7 receptors. The clinical significance of vortioxetine's effect on the serotonin receptors is currently unknown, but in patients with depression, it also appears to improve measures of cognitive function that appear independent of its antidepressant effects. Vortioxetine has a half-life of 66 hours and no active metabolites. The starting and usual dose is 10 mg daily, with a maximum daily dose of 20 mg. Vortioxetine is metabolized by 2D6, and the maximum dose for poor metabolizers or patients taking a strong 2D6 inhibitor is 10 mg daily. Vortioxetine also appears to be associated with a lower incidence of sexual dysfunction. Common adverse effects include nausea, dizziness, vomiting, xerostomia, and diarrhea or constipation.
   3. Trazodone (Desyrel): A serotonin reuptake inhibitor that also blocks serotonin-2A receptors. Trazodone does not cause anticholinergic or cardiotoxic effects, as do the TCAs, but it still causes OH and sedation. Because of its sedative properties (mediated by histamine-1 antagonism), trazodone is often used for insomnia but at lower doses than for depression. It is important to be aware of the potential for priapism, even though it is rare (0.1% or less). Patients should be educated about this risk, and it should be treated as a medical emergency.
   4. Nefazodone (Serzone): Nefazodone is a serotonin-2A antagonist like trazodone, but it also blocks the reuptake of serotonin and norepinephrine. Some have called this class "serotonin antagonist reuptake inhibitors" (serotonin-2A antagonist/reuptake inhibitors). Unlike trazodone, nefazodone has minimal effects on sexual function and is less likely to cause OH. Data suggest that the serotonin-2A–blocking activity makes nefazodone more effective for anxiety associated with depression. Nefazodone's short half-life makes it necessary to administer doses twice daily. The most common adverse effects include sedation, GI concerns, dry mouth, constipation, confusion, and light-headedness. Because nefazodone is a potent inhibitor of 3A4, caution is necessary when using it concomitantly with drugs metabolized by this system. Given the potential for liver toxicity and its black box warning, nefazodone is now considered a second- or third-line agent. Liver function tests must be monitored if nefazodone is used.

H. Mirtazapine (Remeron)
   1. Mirtazapine is an antagonist of presynaptic α_2-autoreceptors and heteroreceptors, which results in an increase in norepinephrine and serotonin in the synapse. In addition, the drug blocks serotonin-2A (resulting in minimal to no sexual dysfunction, anxiety, or sedation), serotonin-3 (no nausea or GI disturbances), and serotonin-2C (weight gain) receptors.

2. Although mirtazapine is better tolerated than the TCAs, it still has a pronounced sedative effect, together with increased appetite, weight gain, constipation, and asthenia.
3. Abnormal liver function tests may occur, and there appears to be a very small risk of neutropenia or agranulocytosis.
4. Lower doses may be sedating, whereas higher doses may cause insomnia.

I. Bupropion
1. Bupropion is primarily an inhibitor of dopamine and norepinephrine reuptake with minimal effects on serotonin. Bupropion's exact mechanism of action remains to be defined. The parent drug blocks dopamine reuptake, whereas the metabolite blocks norepinephrine reuptake.
2. The most important adverse effect is increased risk of seizures. This risk can be minimized by the following:
   a. Avoid use in susceptible patients (e.g., history of seizure disorder, eating disorders).
   b. Do not give more than 150 mg/dose or 450 mg/day (immediate release [IR] or ER) or 400 mg/day (sustained release [SR]).
   c. Avoid dosage titration more often than every 4 days for SR or ER and every 3 days for IR.
   d. The SR and ER products may also cause fewer adverse effects; they have largely replaced the IR tablets.
3. The most common adverse effects include insomnia, anxiety, irritability, headache, and decreased appetite. Bupropion may also increase energy and cause psychosis in susceptible individuals. As noted previously, bupropion may actually improve sexual function; thus, it may be useful in patients not tolerating other agents for this reason. Bupropion has also been used for attention-deficit/hyperactivity disorder and may help with concentration.

J. Tricyclic Antidepressants
1. TCAs are effective, but adverse effects have limited their use. Now that newer agents with more tolerable adverse effect profiles are available, TCAs are used less often. TCAs have several off-label uses such as treatment for pain syndromes, migraine prophylaxis, and anxiety disorders.
2. TCAs block serotonin and norepinephrine uptake. Tertiary amines such as amitriptyline and imipramine are more potent for serotonin uptake and are metabolized to active secondary amines. The corresponding secondary amines (nortriptyline and desipramine, respectively) are more selective for norepinephrine and have less anticholinergic activity.
3. TCAs have α-adrenergic blockade, antihistaminic effects, and anticholinergic effects, leading to orthostasis, sedation, and anticholinergic symptoms, respectively. TCAs can cause sexual dysfunction.
4. TCAs can be cardiotoxic in overdose, causing prolonged QTc intervals and torsades de pointes as well as seizures (Table 9). An ECG should be monitored in patients older than 40 who are initiated on TCAs. An actively suicidal patient should not receive a TCA.

Table 9. Adverse Effect Profile of Commonly Used TCAs

Drug	Anticholinergic	Sedation	Orthostatic Hypotension	Cardiotoxicity
Tertiary amines				
Amitriptyline	High	High	Moderate	High
Imipramine	Moderate	Moderate	High	High
Secondary amines				
Desipramine	Low	Low	Moderate	Moderate
Nortriptyline	Moderate	Moderate	Low	Moderate

5. TCAs are not recommended in patients with cardiac disease or seizure disorders. Patients at risk of OH are at increased risk of falls if they take these agents, and appropriate caution should be taken.
6. TCA serum concentrations can confirm adherence or toxicity. However, this is an infrequent clinical practice.
7. A withdrawal syndrome occurs if these drugs are discontinued too quickly. Symptoms reflect the reversal of anticholinergic effects and include lacrimation, nausea, and diarrhea, with insomnia, restlessness, and possible balance problems. Gradual dose reductions help reduce these symptoms.

K. Monoamine Oxidase Inhibitors
1. MAOIs block the enzyme responsible for the breakdown of certain neurotransmitters, such as norepinephrine. There are two forms of this enzyme (MAO-A and MAO-B), and drugs can block one or both of them.
2. Nonselective MAOIs (isocarboxazid, phenelzine, and tranylcypromine) are available in the United States.
3. Patients taking MAOIs must be educated and monitored to avoid foods high in tyramine (e.g., aged cheese, preserved meats, wine, beer) because of the potential for precipitating a hypertensive crisis. A dietary consultation can be helpful in this respect.
4. Drug interactions with MAOIs are considerable and include over-the-counter decongestants, antidepressants, stimulants, and antihypertensives. When changing a patient from another antidepressant to an MAOI, it is prudent to wait 2 weeks after the antidepressant is discontinued before initiating the MAOI (except for fluoxetine, in which case the waiting period should be 5–6 weeks, and vortioxetine is 3 weeks) to avoid serotonin toxicity. When a patient is changed from an MAOI to another antidepressant, a 2-week washout period is usually adequate.
5. Selegiline (MAO-B inhibitor) is available in a patch formulation for depression. Selegiline is available in doses of 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours. Once the dose reaches 9 mg/24 hours, an MAOI diet is required. How this drug compares with other antidepressants remains unknown.

L. Antidepressants and Suicidality: All antidepressants have an FDA black box warning for an increased risk of suicidal thinking and behaviors in children, adolescents, and young adults (up to 24 years of age). Risk is highest at treatment initiation or dose adjustment. Other signs to watch for include agitation and anxiety (activation syndrome) and other symptoms that are unlike the patient's presenting symptoms of depression. A medication guide must be distributed before antidepressants are dispensed. The warning should not preclude antidepressant use in children, adolescents, and young adults because suicide is the second leading cause of death in this population. The results of three meta-analyses show that antidepressants decrease suicidal thoughts and acts in patients age 25–64 and decrease suicidal acts in those older than 65. The number needed to treat for an SSRI in an adolescent with depression to prevent suicidal thoughts and acts is 4–10.

M. Partial Response to Antidepressant Treatment
1. Ensure the patient is adherent and has received a therapeutic trial (as defined in section D2 earlier) of medication.
2. Patients can either be changed to a new antidepressant or receive adjunctive therapy. The 2016 CANMAT guidelines have a helpful algorithm and tables (see References section).
3. An antidepressant with a different mechanism of action can be added (e.g., bupropion or mirtazapine to an SSRI or SNRI). Data are not strong for this practice. Use caution when combining agents to avoid potential serotonin syndrome with at-risk agents.
4. SGAs (or atypical antipsychotics) may be used as adjuncts to antidepressant therapy. Almost all SGAs have been used, but only aripiprazole, brexpiprazole, and quetiapine ER have received FDA approval for this indication. Evidence also supports the use of risperidone. Olanzapine in combination with fluoxetine is also approved, but specifically for treatment-resistant depression.

5. Ketamine infusions are used off-label for depression and suicidality, particularly in patients who are not responsive or who are only partly responsive to antidepressants.
6. Other adjuncts include lithium, liothyronine, stimulants (including methylphenidate and modafinil), and buspirone.

N. Treatment-Resistant Depression
   1. Has many definitions; usually defined as inadequate response to at least two antidepressants
   2. FDA-approved treatment options
      a. Olanzapine plus fluoxetine: Initial dosing is 6 mg/25 mg once daily; usual dosing is 6–18 mg/25–50 mg daily.
      b. Esketamine (intranasal; Spravato)
         i. Approved for use in conjunction with an oral antidepressant
         ii. Also approved for major depression with suicidality
         iii. Mechanism of action: NMDA (*N*-methyl-D-aspartate) antagonist
         iv. Onset for treating depression symptoms is within hours.
         v. Dosing occurs in two phases: twice weekly during the induction phase, which lasts for 2 weeks, followed by the maintenance phase, in which dosing is weekly for 4 weeks and then every 1–2 weeks thereafter.
         vi. Carries black box warnings for sedation, dissociation, abuse and misuse (CIII), and suicidal thoughts and behaviors
         vii. Common adverse reactions: Increased blood pressure, dissociative reactions including derealization and depersonalization, sedation, dizziness, anxiety, nausea, vomiting, and dysgeusia. Long-term use or misuse of ketamine has also been associated with ulcerative or interstitial cystitis. This has not been observed with esketamine in clinical trials but should be monitored.
         viii. Only available through a REMS program in which patients must be enrolled. Only approved pharmacies can dispense, and agent must be administered in a certified health care setting where patients are observed for at least 2 hours after administration. During this time, mental status and blood pressure must be monitored. Patients cannot drive until the following day.

Patient Cases

Questions 9–11 pertain to the following case.

A 26-year-old man with a history of type I bipolar disorder presents to the inpatient unit. His wife found that he was withdrawing their life savings from the bank. He states that he is the perfect candidate for the presidency. He is hyperverbal and has not slept in the past 48 hours. He is placed on an involuntary mental health hold for control of his manic symptoms. He has a history of nonadherence to medications and currently takes none. His last hospitalization was 2 months ago, when he had significant depressive symptoms and suicidal ideation. He has three or four hospitalizations per year, and his history of medication trials includes olanzapine and lamotrigine. He has also been given a diagnosis of hepatitis C with AST 175 U/L and ALT 186 U/L.

9. Which mood stabilizer is most appropriate for this patient at this time?
   A. Carbamazepine.
   B. Divalproex sodium.
   C. Lamotrigine.
   D. Lithium.

Patient Cases *(Cont'd)*

10. Which treatment-emergent adverse effect would be of most concern and would require immediate evaluation if he were prescribed lithium?
    A. Hypothyroidism.
    B. Coarse tremor.
    C. Severe acne.
    D. Weight gain.

11. Three months later, his condition has been stable on lithium 900 mg/day. However, during a clinic visit, he is confused and slurring his words. His current lithium serum concentration is 1.9 mEq/L. He has been taking lisinopril and atorvastatin again for his hypertension and dyslipidemia for 2 months. He takes zolpidem for sleep. He began running a week ago. He has been replacing fluids using an oral rehydrating solution (Gatorade) and taking ibuprofen around-the-clock for pain. His other medications include lisinopril, atorvastatin, and zolpidem. Which most likely contributed to this patient's current clinical situation?
    A. Gatorade.
    B. Ibuprofen.
    C. Lisinopril.
    D. Zolpidem.

12. A 36-year-old woman (BMI 20 kg/m^2) with type I bipolar disorder presents to your clinic tearful, with a 2-week history of depressed mood, anhedonia, insomnia, feelings of worthlessness, and loss of appetite. She has passive thoughts of suicide, but no concrete plan. She currently takes lithium, with a trough serum concentration of 1.1 mEq/L. Which medication would be best to treat her current episode?
    A. Divalproex sodium.
    B. Lamotrigine.
    C. Quetiapine.
    D. Venlafaxine.

III. BIPOLAR DISORDER

A. Overview of Bipolar Disorder
    1. The *DSM-5* defines bipolar disorder by the experience of a manic or hypomanic episode. Mania can be thought of as the affective opposite of depression. Consult the *DSM-5* for a complete description of the diagnostic criteria. A manic episode is characterized by at least 1 week (or any duration, if hospitalization needed) of an abnormal and persistently elevated, expansive, or irritable mood accompanied by an abnormally and persistently increased goal-directed activity. The patient must also have three of the following symptoms (four if mood is irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased hyperactivity or psychomotor agitation, and involvement in high-risk activities without respect to the consequences. A hypomanic episode is a milder form of mania. This episode must exist for 4 days or longer and is not severe enough to warrant hospitalization, is not severe enough to cause marked social or occupational impairment, and is not associated with psychosis.

2. The *DSM-5* includes two types of bipolar disorder (I and II):
   a. Bipolar I: Chronic disorder marked by one or more manic or mixed episodes. Although major depressive episodes are not necessary for the diagnosis, most patients have depressive episodes.
   b. Bipolar II: Chronic disorder marked by one or more major depressive episodes, accompanied by at least one hypomanic episode
   c. Cyclothymic disorder: Several periods of hypomania and mild depression, none of which meet the criteria for mania or major depressive episode
   d. Rapid cycling: At least four episodes of mania or depression in 1 year
3. Bipolar disorder, particularly type II bipolar disorder, is often misdiagnosed as major depression. The diagnosis is important because the two conditions are treated differently.

B. Lithium for Bipolar Disorders
1. The exact mechanism of action for lithium is unknown, but it appears to be neuroprotective.
2. Lithium continues to be the gold standard for treating type I bipolar disorder. Lithium is effective for the manic and depressive components. Although lithium is not a particularly good antidepressant as monotherapy in unipolar depression, it is effective in patients with bipolar disorder. Lithium has evidence for reducing suicidality when used for bipolar disorder.
3. Antimanic effects can occur in 1–2 weeks. Most clinicians use antipsychotics or benzodiazepines as adjunctive therapy during this period to cover the agitation and other symptoms. Antidepressant effects may take 6–8 weeks.
4. Pharmacokinetics: Lithium's half-life is 20–24 hours. Lithium is excreted 95% unchanged by glomerular filtration, and anything that alters the glomerular filtration rate affects its clearance. Pharmacokinetic methods are available for early prediction of doses, but waiting 5–6 days for steady state seems to work just as well.
5. Initial dosing is 600–900 mg/day in divided doses, and dosing is then titrated according to response and tolerability. Maintenance doses are based on serum concentrations, symptom relief, and the occurrence of adverse effects.
6. A pre-lithium workup includes a complete blood cell count, electrolytes, renal function, thyroid function tests, urinalysis, ECG, and pregnancy test for women of childbearing age.
7. Monitoring: Serum concentrations must be monitored. Most clinicians will aim for concentrations of 0.8–1.2 mEq/L in acute mania and 0.6–1.0 mEq/L during maintenance. Concentration-response data are based on 12-hour postdose concentrations, so concentrations should be ordered in the morning 12 hours after the last evening dose. Renal function tests, thyroid function tests, and a urinalysis should be done every 6–12 months.
8. Adverse effects are common with lithium, particularly during therapy initiation or after dose changes. Table 10 lists common adverse effects.
9. Symptoms of lithium toxicity include lethargy, coarse tremor, confusion, seizures, and coma and may even result in death. Patients who present to urgent care on lithium therapy should always be monitored for lithium toxicity before any medication adjustments. Lithium concentration and sodium/renal function should be obtained so that lithium concentrations can accurately be estimated. Treatment of choice for severe lithium toxicity is hemodialysis.

Table 10. Adverse Effects Associated with Lithium

Problem	Potential Interventions
Rash or ↑ psoriasis	Discontinue the drug temporarily or permanently
Tremor	Reduce dose (Cp); add β-blocker
CNS toxicity (e.g., agitation, confusion)	Reduce dose (Cp)
GI (nausea, vomiting, diarrhea)	Reduce dose; try ER product, split doses
Hypothyroidism	Give levothyroxine; discontinue lithium, if necessary
Polydipsia or polyuria	Reduce dose, manage fluid intake; single bedtime dosing helps
Interstitial fibrosis, glomerulosclerosis	Keep dose at lowest effective concentration; avoid dehydration
Teratogenicity	Avoid during first trimester, if possible

Cp = plasma concentration.

10. Pregnancy: Lithium passes the placental barrier and has been associated with cardiac and other abnormalities, including Ebstein abnormality. However, it may have a lower risk than previously thought. Women of childbearing age should be counseled on its potential effects. Risks of discontinuing lithium therapy must be weighed against potential effects on the fetus when making decisions regarding lithium therapy during pregnancy.
11. Table 11 lists additional situations to consider during lithium therapy.

Table 11. Situations to Consider During Lithium Therapy

Situation	Factors	Results
Drug interactions	Diuretics	
	Thiazides	↑ Li Cp; avoid use to reduce toxicity
	Furosemide	↑ Li Cp; avoid use to reduce toxicity
	Amiloride	Little effect
	NSAIDs	↑ Li Cp; avoid use to reduce toxicity
	Theophylline	↓ Li Cp
	ACEIs	↑ Li Cp; avoid use to reduce toxicity
	Neuromuscular blockers	Li prolongs action
	Neuroleptics	Li may potentiate EPS
	Carbamazepine	↑ CNS toxicity
Thyroid	Li ↓ synthesis and release of thyroid hormone	Hypothyroidism
Pregnancy	↑ GFR	↓ Li Cp (first and second trimesters; third trimester may return to baseline)
Aging	↓ GFR	↓ Li requirements
	↑ Sensitivity to ADRs	Li toxicity
↓ Renal function	↓ GFR, ↑ creatinine and BUN	↑ Li Cp
Dehydration, salt restriction, and extrarenal salt loss	↑ Sodium reabsorption	↑ Li Cp

ACEI = angiotensin-converting enzyme inhibitor; ADR = adverse drug reaction; BUN = blood urea nitrogen; EPS = extrapyramidal symptoms; GFR = glomerular filtration rate; Li = lithium; NSAID = nonsteroidal anti-inflammatory drug.

C. Anticonvulsants for Bipolar Disorder: These are also considered mood-stabilizing drugs that reduce manic and depressive episodes. See the Neurology chapter for additional drug-specific details.
   1. Divalproex/valproic acid (Depakene, Depakote, Depacon, Stavzor):
      a. As effective as lithium in acute and prophylactic management. Divalproex appears to be good for rapid cyclers but may not be as effective during depressive episodes. Divalproex is also beneficial for patients with dysphoric mania, mixed episodes, or a history of SUD.
      b. Black box warnings:
         i. Hepatotoxicity: Can result in death. Most common during the first 6 months of therapy. Risk is higher in children younger than 2 years. Liver function tests should be monitored routinely at the start of therapy and routinely thereafter, particularly during the first 6 months.
         ii. Mitochondrial disease: Patients with mutations of the mitochondrial DNA polymerase gamma (*POLG*) gene, such as Alpers-Huttenlocher syndrome, are at an increased risk of valproate-induced liver failure and death. Valproate is contraindicated in these patients.
         iii. Fetal risk: Valproate can cause major congenital malformations, particularly neural tube defects (including spina bifida), decreases in IQ scores, and neurodevelopmental disorders after in utero exposure. Valproate should not be used in women of childbearing age unless other medications have failed to provide adequate therapeutic benefit. Women of childbearing age who are taking valproate should also be receiving effective contraception.
         iv. Pancreatitis: Life-threatening pancreatitis can occur but is uncommon (less than 5%). Life-threatening pancreatitis can recur with reinitiation of valproate, so valproate should not be reinitiated.
      c. Reference serum concentrations are 50–125 mcg/mL, but the exact concentration necessary for therapeutic effect is not well established. Serum concentrations should be interpreted in connection with clinical response. Therapeutic effects are usually seen with doses of 1.5–2.5 g/day. The serum concentration can be checked 3–5 days after initiation or a change in dose. Hypoalbuminemia increases the risk of increased free concentrations. Treatment nonresponse is common if the dose is too low; however, the free fraction increases as the serum concentration is increased (above 100–125 mcg/mL). Dose-related adverse effects that occur at serum concentrations greater than 80 mcg/mL include neurotoxicity, sedation, hair loss, and thrombocytopenia. The ER preparation has lower bioavailability than the enteric-coated preparation. The dose should be increased by 8%–20% when converting to the ER product.
   2. Carbamazepine (Tegretol, Tegretol XR, Equetro): Effective for acute mania and maintenance therapy, particularly in patients with a history of head injury. Equetro is FDA approved for acute manic and mixed episodes. The serum concentration does not correlate well with therapeutic effect; however, it can be used to monitor for adherence and toxicity. Carbamazepine can also be added to lithium for patients who have not responded to monotherapy, but this increases the risk of neurotoxicity (see Lithium section earlier) and is not commonly done in practice. As a reminder, carbamazepine is a strong inducer of CYP metabolism. Carbamazepine also autoinduces its own metabolism and thus can take time to come to steady state. See the Neurology chapter for more information.
   3. Lamotrigine (Lamictal):
      a. Has been approved for maintenance therapy. Lamotrigine appears particularly effective in preventing future depressive episodes of bipolar disorder. Lamotrigine is less effective than other mood stabilizers for preventing the manic phase.
      b. A Stevens-Johnson rash occurs in about 0.3% of adults and 1% of children. Lamotrigine must be discontinued if a rash occurs and should never be rechallenged. Risk increases with rapid dose titrations, high doses, young age, and concurrent use of valproic acid. The rash is most common within the first 2–8 weeks of therapy. If the medication is missed for greater than 5 half-lives (about 5 days), it must be retitrated from the starting dose.

c. The dose titration must be halved if lamotrigine is given with valproate and doubled if given with carbamazepine because of drug-induced alterations in lamotrigine metabolism. The titration period is lengthy, so the onset of therapeutic effect can be delayed. For this reason, lamotrigine is not helpful in the acute setting.
d. Lamotrigine has been associated with aseptic meningitis in adult and pediatric patients. Patients who experience headache, fever, chills, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, drowsiness, or confusion while taking lamotrigine should contact their health care professional right away. In 15 of 40 identified cases of aseptic meningitis, symptoms returned when patients were rechallenged with lamotrigine. Symptoms have occurred 1–42 days after the drug was started, and many patients required hospitalization.
e. A rare but life-threatening immune reaction called hemophagocytic lymphohistiocytosis (HLH) can occur with lamotrigine. Onset is usually within the first few weeks of therapy. Symptoms may include fever, rash, hepatosplenomegaly, organ system dysfunction, and blood dyscrasias. Patients who develop HLH should be taken off lamotrigine and changed to alternative treatment.

4. Other anticonvulsants, including levetiracetam, oxcarbazepine, and topiramate, are used for bipolar disorder, but data regarding their efficacy are scarce. Data for gabapentin suggest it is ineffective.

D. Antipsychotics for Bipolar Disorder: Antipsychotics, particularly SGAs, have mood-stabilizing properties. Antipsychotics can be used alone or with anticonvulsant mood stabilizers to treat bipolar symptoms. Metabolic adverse effects associated with antipsychotic use should be considered when medications are administered long term (see the Schizophrenia section).
1. Acute treatment: Antipsychotics treat acute symptoms of mania, including aggression and irritation, and any co-occurring psychosis. Antipsychotics are often combined with a traditional mood stabilizer for severe symptoms. All SGAs have received FDA approval for use in acute mania or mixed episodes except for brexpiprazole, clozapine, iloperidone, lumateperone, and lurasidone. For acute mania, the Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders (CANMAT/ISBD) guidelines include aripiprazole, asenapine, cariprazine, paliperidone (more than 6 mg daily), quetiapine, and risperidone among the first-line agents.
2. Bipolar depression: Cariprazine, quetiapine, and lurasidone are approved for bipolar depression. Olanzapine is also approved for bipolar depression when combined with fluoxetine. Data for aripiprazole suggest it is ineffective for bipolar depression.
3. Maintenance treatment: The LAI antipsychotic formulations Risperdal Consta and Abilify Maintena have been approved for use in bipolar maintenance as monotherapy. The CANMAT/ISBD guidelines also recommend olanzapine and quetiapine.

E. Benzodiazepines for Bipolar Disorder: Benzodiazepines are acutely helpful for agitation but not for the core symptoms, nor do they prevent relapses. Benzodiazepines are particularly useful for insomnia, hyperactivity, and agitation. Lorazepam or diazepam is often used in the acute setting. Long-term therapy is not recommended.

F. Antidepressants for Bipolar Disorder:
1. Use of antidepressants in bipolar disorder is controversial, given concern for switching to the manic phase, particularly in patients with type I bipolar disorder. The risk appears greater with TCAs and SNRIs than with SSRIs or bupropion. Because individual patients with bipolar disorder may benefit from antidepressants, the ISBD stopped short of recommending against any use of antidepressants. However, antidepressants should not be used as monotherapy, and their use should be minimized in general. Antidepressants should not be used in bipolar depression if symptoms of mania are also present. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trials found

no statistically significant increased episodes of depression in patients taking mood stabilizers who discontinued their antidepressants. Patients with bipolar disorder taking mood stabilizers who received either paroxetine or bupropion were no more likely to achieve remission or have a durable recovery than those receiving placebo. These patients were also no more likely to switch to a manic phase.

2. Fluoxetine in combination with olanzapine is approved to treat depression associated with type I bipolar disorder.

G. Type II Bipolar Disorder: The depressive phase tends to be more debilitating. Patients are usually functional during hypomanic episodes. Treatment therefore focuses on the depressive phase. Lithium is a first-line agent, but it may not achieve remission as monotherapy and takes time to relieve symptoms. Quetiapine is preferred for acute symptom treatment. Lurasidone can also be used. Lamotrigine is a reasonable alternative for longer-term symptom control, but because of its slow titration schedule, it is not useful in the acute setting. Other mood stabilizers can be used but may not be as efficacious as for type I bipolar disorder. Antidepressants are used more commonly but should be used with caution, and never as monotherapy. Olanzapine and fluoxetine may thus be an option.

Patient Cases

13. A recent Iraq war veteran has been treated successfully with paroxetine for his major depression for the past 3 weeks. He presents to the clinic experiencing nightmares, "feeling on edge all the time," and having flashbacks of his time in the war. He is evaluated and given a diagnosis of posttraumatic stress disorder (PTSD). He has no history of substance dependence and no significant medical history. Which recommendation is most appropriate for this patient at this time?

    A. Continue paroxetine because it treats both PTSD and major depression.

    B. Discontinue paroxetine and initiate sertraline, which treats both PTSD and major depression.

    C. Continue paroxetine and add lorazepam for the anxiety symptoms.

    D. Discontinue paroxetine and initiate buspirone for the anxiety symptoms.

14. A 48-year-old man has newly diagnosed GAD. He cannot sleep at night. He reports frequent headaches, which he treats with ibuprofen. His family history is positive for depression (his mother) and anxiety (his sister). Which medication would be best for long-term symptom resolution?

    A. Alprazolam.

    B. Buspirone.

    C. Paroxetine.

    D. Pregabalin.

15. A 27-year-old woman with panic disorder is having difficulty functioning at work. She had her first panic attack while getting a cup of coffee. She felt she was having a heart attack and was seen at the local emergency department, where physical causes were ruled out. She has had several subsequent episodes. She cannot predict when or where they will occur. Her absenteeism from work is high, and she is concerned about her job. Her medical history is otherwise unremarkable. Which medication would most quickly allow her to return to work?

    A. Alprazolam.

    B. Buspirone.

    C. Paroxetine.

    D. Venlafaxine.

Patient Cases *(Cont'd)*

16. A 21-year-old woman has newly diagnosed OCD. She cannot hold a job because she is so consumed by her obsessions and compulsions. She is convinced that her obsessions are reality. Which medication is most appropriate to initiate?
    A. Bupropion.
    B. Desipramine.
    C. Fluoxetine.
    D. Mirtazapine.

IV. ANXIETY AND RELATED DISORDERS (OCD, PTSD)

A. Overview of Anxiety Disorders
    1. GAD is characterized by 6 months or more of excessive worry or anxiety, generally with an unidentified cause.
    2. Panic disorder is characterized by discrete periods of sudden, intense fear or terror and feelings of impending doom. This is followed by continued worry about the implications of the panic attacks. Usually, the precipitating cause is unknown, but the patient can become conditioned to believe it is attributable to some environmental cause.
    3. Agoraphobia: Intense fear in two or more settings (mostly in the open or in public). These settings include using public transportation, being in open spaces, being in enclosed spaces, standing in line or being in a crowd, and being outside the home alone.
    4. Social anxiety disorder is characterized by marked and persistent fear and anxiety in social or performance situations that are recognized as excessive or unreasonable. These situations are either avoided or endured with intense anxiety.
    5. Specific phobias are characterized by intense fear or anxiety induced by a specific object.
    6. Obsessive-compulsive disorder (OCD), which used to be classified as an anxiety disorder, now has its own designation. Obsessions are recurrent and persistent thoughts, urges, or images that are intrusive and unwanted (e.g., fear of contamination, doubts, need for symmetry). Compulsions are ritualistic behaviors (e.g., washing the hands, combing the hair, cleaning the house) that relieve anxiety from the obsessions.
    7. PTSD, which also used to be classified as an anxiety disorder, has been moved to a category titled "Trauma- and Stressor-Related Disorders." PTSD follows a traumatic event. PTSD is characterized by increased arousal and avoidance of stimuli that approximate the original traumatic event.
    8. See the *DSM-5* for more details on each specific disorder.

B. Pharmacotherapeutic Options for Anxiety and Related Disorders
    1. Benzodiazepines: These drugs have anxiolytic properties, and some have preventive efficacy for panic attacks. Benzodiazepines are not appropriate for all anxiety disorders (see the individual disorders for role). Depending on the agent, the onset can be quite rapid, as outlined in the text that follows. The high-potency, short-half-life agents are the most rapid acting. They are effective for treating the acute somatic and autonomic symptoms of anxiety but do not adequately address the underlying cognitive and psychological pathology.
        a. Pharmacologically, benzodiazepines share, to various degrees, five properties: (1) anxiolytic, (2) hypnotic, (3) muscle relaxation, (4) anticonvulsant, and (5) amnesic actions. Tolerance of the anxiolytic action is uncommon. Benzodiazepines are differentiated by their half-life (plus or minus active metabolites) and potency. If they are thought of as short-half-life/high-potency versus long-half-life/lower-potency drugs, the following distinctions can be made:

i. Short half-life/high potency: These drugs are usually more rapid acting and provide quicker symptom control. However, tolerance of the hypnotic effect develops rapidly, withdrawal problems are common, and interdose breakthrough symptoms can occur. These are often used for acute management and later withdrawn after maintenance medication is optimized.
ii. Long half-life/low potency: These drugs produce longer-lasting effects throughout the day, and although withdrawal symptoms may be less pronounced, they do occur. Interdose breakthrough symptoms are less likely; however, more "hangover" symptoms occur in the morning. These agents can accumulate in older adult patients.
iii. Table 12 compares the half-lives and potencies of the five main/most commonly prescribed benzodiazepines for anxiety disorders.

Table 12. Half-lives and Potency of the Most Commonly Prescribed Benzodiazepines

Agent	Half-Life (hr)	Equivalent Dose (mg)
Alprazolam (Xanax)	6–12	0.5
Chlordiazepoxide (Librium)	5–30[a]	25
Clonazepam (Klonopin)	20–50	0.5
Diazepam (Valium)	20–100[b]	10
Lorazepam (Ativan)	10–18	1

[a]Active metabolites: Desmethylchlordiazepoxide, demoxepam (half-life 14–95 hr), desmethyldiazepam (half-life 71–100 hr).

[b]Active metabolite: Desmethyldiazepam (half-life 71–100 hr).

b. Primary issues associated with benzodiazepines are tolerance and dependence. Tolerance of the hypnotic actions occurs within days. Dependence occurs within weeks to months of continued use. Abrupt cessation can lead to withdrawal and may be life threatening. Hence, it is generally recommended that treatment periods be restricted to 3–4 weeks, or about the time an antidepressant takes to begin to working for anxiety symptoms. After this time, the patient is tapered off the benzodiazepine to avoid withdrawal symptoms. If the patient has taken the benzodiazepine for a significant time, it can take several months to more than 1 year to complete. In practice, many patients go on to use benzodiazepines for long periods. Often, these patients are not in remission, despite treatment with maintenance medications. Minimize use of benzodiazepines in patients with a history of SUD or risk factors for SUD because of the risk of misuse. Information on benzodiazepine tapers can be found at deprescribing.org.

2. Antidepressants: SSRIs are also effective for several anxiety disorders and are the agents of choice for long-term treatment of anxiety disorders. Venlafaxine has been approved for GAD and social anxiety disorder. Duloxetine is also approved for GAD. Some initial symptoms may be improved within days, but the full benefit of treatment may take weeks, as for depression treatment. TCAs have preventive efficacy for panic disorder and anxiolytic activity. About 25% of patients with anxiety disorders (particularly GAD and panic disorder) have a hyper-stimulatory response to antidepressants, which can be confused with a worsening of the anxiety symptoms. This response is more common when therapy is first begun. Using low doses at first can help. Antidepressants can also help with anxiety that accompanies depression.
3. Buspirone: This drug has anxiolytic properties, but clinicians are divided on its real value in treating GAD. Buspirone has little efficacy for other anxiety disorders. The main drawback to buspirone is its long onset of action (weeks). In the meantime, the anxiety must be covered with another agent. Some clinicians use short-term benzodiazepines as a bridge until buspirone takes effect. Buspirone must also be dosed two or three times daily as scheduled (not prn), which decreases the chances for adherence. Buspirone should only be scheduled and never used as needed.

4. Miscellaneous agents
    a. β-Blockers are sometimes used to block the peripheral symptoms of panic disorder or performance anxiety.
    b. MAOIs can be effective for panic disorder when the patient also has atypical depression. However, MAOIs are seldom used because of the potential for serious adverse effects.
    c. Antihistamines with sedating properties (e.g., hydroxyzine) can help reduce physical symptoms of anxiety.
    d. Barbiturates are seldom used. They are often less effective and can be lethal if taken in overdose.
    e. Antipsychotics are not considered first-line agents for anxiety disorders. Selected SGAs can be useful add-on therapy for OCD, GAD, and PTSD.
5. CBT should be an integral part of any therapeutic plan for anxiety disorders.

C. Recommended Therapy for Specific Anxiety and Related Disorders
1. GAD
    a. Antidepressants: These are considered first-line agents. These include the SSRIs (escitalopram, paroxetine [IR and CR], and sertraline) and the SNRIs (duloxetine and venlafaxine XR).
    b. Benzodiazepines: This class of drugs is rapidly effective; if possible, try to discontinue in 3–4 weeks or once the patient has remittance of symptoms. Benzodiazepines are more effective against somatic symptoms than against the underlying pathology. Evidence is strongest for alprazolam, diazepam, and lorazepam.
    c. Buspirone: Can be considered when benzodiazepines should be avoided (e.g., in patients with a history of SUD); takes 2–4 weeks to be effective. Buspirone is considered a second-line agent.
    d. Pregabalin: Depending on the guidelines, it is considered a first- or second-line agent (behind antidepressants). Does not carry an FDA indication for treating any form of anxiety. Limited data suggest similar efficacy with venlafaxine and benzodiazepines. Pregabalin can also be used as an adjunct.
    e. Not effective: β-Blockers
    f. CBT or another type of psychotherapy should be included with pharmacotherapy.
    g. In treatment-refractory patients, augmentation with aripiprazole, quetiapine, olanzapine, or risperidone can be tried.
2. Panic disorder
    a. Antidepressants: First-line therapy. These include all the SSRIs and venlafaxine XR.
    b. Benzodiazepines: High-potency agents; effective; rapid onset; evidence is strongest for alprazolam, clonazepam, diazepam, and lorazepam
    c. Not effective: Buspirone, β-blockers, antihistamines, trazodone. Bupropion is considered third line in some guidelines and is not recommended in others.
    d. CBT and other psychotherapies are effective.
    e. Patients with panic disorder tend to have a higher sensitivity to physical adverse effects. For this reason, these patients should be initiated on low doses of antidepressants – as low as 25 mg of sertraline or 10 mg of paroxetine.
3. OCD
    a. Serotonergic agents are effective – SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). Depending on guidelines, clomipramine is considered a first- or second-line agent. Because of its adverse effect profile, clomipramine is typically used clinically as second line. Patients tend to require doses of antidepressants at the higher end of the dosing range.
    b. CBT is as effective as pharmacotherapy and is considered the treatment of choice for adolescents and adults with mild OCD.

c. Alone, SSRIs often fail to control OCD completely. Not many other drugs help. Augmentation with haloperidol or an SGA (aripiprazole, olanzapine, quetiapine, or risperidone) may help. In general, high antipsychotic doses need to be used.

4. PTSD
   a. PTSD can be combat or non–combat related, and response to therapy may vary depending on the source of trauma.
   b. Psychotherapy is considered the cornerstone of treatment. Effective methods incorporate CBT, including exposure therapy and trauma-based cognitive processing therapy.
   c. Medications are considered adjuncts to psychotherapy. They are preferred if psychotherapists are not readily available or if a patient declines psychotherapy.
   d. SSRIs (sertraline and paroxetine are FDA approved, but evidence is also strong for fluoxetine) and venlafaxine XR are considered first-line agents.
   e. Augment with other agents to treat specific symptoms.
      i. Prazosin is commonly used for PTSD-associated nightmares, though evidence on its efficacy is conflicting.
      ii. Anticonvulsants can be used for aggression, anger, and depression (carbamazepine, lamotrigine, topiramate). Valproic acid is not considered effective.
      iii. Atypical antipsychotics can be used for psychotic symptoms (aripiprazole, quetiapine, risperidone). Some guidelines recommend against the use of olanzapine because of its high incidence of metabolic syndrome.
   f. Benzodiazepines are sometimes used acutely for sleep disturbances, but use should be very limited. Most data analyses indicate a lack of efficacy. Benzodiazepines have dissociative and disinhibiting properties and may worsen non-hyperarousal symptoms. Benzodiazepines may also interfere with the fear-conditioning aspects of psychotherapy. The VA/DoD guidelines recommend against the use of benzodiazepines.
5. Social anxiety disorder
   a. CBT is the most important modality.
   b. Antidepressants: First-line medication for treatment; SSRIs (paroxetine [IR and CR] and sertraline are FDA approved, but evidence also supports the use of escitalopram, fluvoxamine [IR and CR]), and venlafaxine XR (FDA approved). Response to antidepressants tends to be slow (up to 12 weeks) and has a flat dose-response curve.
   c. Benzodiazepines (alprazolam and clonazepam) are considered second-line agents, but use should be minimized, given the risk of SUDs among patients with social anxiety disorder.
   d. Anticonvulsants: Pregabalin is considered a first-line agent, and gabapentin is a second-line agent.
6. Specific phobias
   a. Not treated with medication
   b. Systematic desensitization and other behavioral approaches often effective

Patient Case

Questions 17–19 pertain to the following case.

A 38-year-old kindergarten teacher presents to the clinic today with noticeable dark circles under her eyes. She has difficulty with sleep, mainly with staying asleep. It takes her about 20 minutes to fall asleep, but after about 2 hours, she wakes up and cannot fall asleep again for several hours. This pattern has negatively affected her job performance, and she feels tired all the time. She once took diphenhydramine for sleep but had to miss work because of extreme drowsiness in the morning. She wonders whether she could take any other medications. Her other medical problems include hypothyroidism (levothyroxine 125 mcg at bedtime), hypertension (hydrochlorothiazide 25 mg in the morning), chronic back pain (ibuprofen 800 mg three times daily), and MDD (citalopram 20 mg in the morning).

17. Which agent is most likely contributing to her insomnia?
    A. Citalopram.
    B. Hydrochlorothiazide.
    C. Ibuprofen.
    D. Levothyroxine.

18. Which medication used for insomnia is most appropriate to recommend for this patient?
    A. Eszopiclone.
    B. Trazodone.
    C. Temazepam.
    D. Zaleplon.

19. Which adverse effect of zolpidem would carry the greatest potential for harm in her?
    A. Orthostasis.
    B. Disorientation.
    C. Abnormal behaviors while asleep.
    D. Seizures with high doses of the drug.

V. INSOMNIA

A. Normal Sleep Patterns and Neurochemistry/Physiology of Sleep
   1. About one-third of a life is spent in sleep. Optimal sleep duration for most adults to maintain good health is 7–9 hours per 24-hour period. Variation exists among individuals and according to age.
   2. Adverse outcomes, including increased mortality, are associated with both short sleep duration (6 hours or less per 24-hour period) and long sleep duration (more than 9–10 hours per 24-hour period).
   3. The body's circadian rhythm is controlled by both internal and external factors. It sets the sleep-wake cycle at 24.2 hours, which is modified by sensory input (e.g., darkness to signal sleep and brightness to signal wakefulness). The suprachiasmatic nucleus (SCN) is the main control center for sleep, and the retinal ganglion cells send direct signals to the SCN to provide information about light.
   4. The neural networks regulating sleep-wake cycles are located in the brain stem, basal forebrain, and hypothalamus, with projections to the cortex and thalamus.
   5. The reticular activating system maintains wakefulness, and when activity here declines, sleep occurs.
   6. Several neurotransmitters are involved in the sleep-wake cycle. Norepinephrine, acetylcholine, histamine, orexin, and serotonin promote wakefulness. γ-Aminobutyric acid (GABA), adenosine, and melatonin promote sleep.

7. Sleep is divided into two categories: non–rapid eye movement (REM) and rapid eye movement (REM) (see Table 13). They can be characterized by measurements with simultaneous electroencephalograms, electro-oculograms, and electromyograms. These are used to measure sleep latency (time to sleep onset), number of awakenings, number of stage shifts during the night, and latency to REM. These recordings are termed *polysomnography*. Polysomnography is not a routine part of diagnosing insomnia.

Table 13. Sleep Stages

State	Time Spent in State	Characteristics	Purpose
NREM sleep	75%		Rest and rejuvenation
Stage 1	2%–5%	Relaxed wakefulness; purpose is to initiate sleep	
Stage 2	50%	Muscle atonia, low-voltage brain waves; alpha wave activity; low-voltage EEG with sleep spindles and K-complexes	
Stage 3	5%	Slow-wave (delta) activity; deep sleep; restorative sleep	
Stage 4	10%–15%		
REM sleep	25%	Low-voltage, mixed-frequency EEG; low muscle tone; REMs; autonomic fluctuations in heart rate and perspiration; and dreaming reported in 80%–90% of subjects	Unknown
EEG = electroencephalogram; NREM = non–rapid eye movement; REM = rapid eye movement.			

8. Sleep architecture is cyclic and dynamic. Passing from wakefulness to stage 4 non-REM sleep takes about 45 minutes in young adults. REM usually occurs within 90 minutes of falling asleep; at first, REM lasts 5–7 minutes, but it becomes progressively longer through the night. The sleep cycle (non-REM stages 1–4 and REM), which lasts about 70–120 minutes, is repeated four to six times a night.
9. Sleep patterns change with age. Older adult patients experience less delta sleep, REM sleep, and total sleep time. They have more nocturnal awakenings and more total wake time at night. The incidence of insomnia may be as high as 40%.

B. Sleep Disorders
   1. The *DSM-5* recognizes 10 sleep-wake disorders or disorder groups. Among the most common are insomnia disorder, hypersomnia disorder, narcolepsy, breathing-related sleep disorders (including sleep apnea), and parasomnias (including non-REM sleep arousal disorders such as sleepwalking type or nightmare disorders, and restless legs syndrome).
   2. Insomnia occurs in 35%–50% of the adult population. Risk factors include increasing age, female sex, comorbid disorders (medical, psychiatric, sleep, and SUD), shift work, and possibly unemployment and lower socioeconomic status. The course is often chronic, with persistence of one to several years in 50%–85% of people.
   3. Insomnia has a reciprocal relationship with other psychiatric diagnoses. Many patients with insomnia have comorbid anxiety disorders, mood disorders (including depression and bipolar disorder), psychotic disorders (schizophrenia and schizoaffective disorder), dementia, attention deficit disorder, and personality disorders. Insomnia can also be a symptom of psychiatric disorders such as anxiety, depression, and bipolar disorder and can exacerbate or precipitate episodes.
   4. Insomnia causes significant morbidity, including impaired driving and occupational accident risk.
   5. Insomnia disorder (*DSM-5*)
      a. Dissatisfaction with sleep quantity or quality, associated with one or more of the following symptoms:

i. Difficulty initiating sleep (also called onset or initial insomnia)
ii. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings (also called sleep maintenance or middle insomnia)
iii. Early morning awakening with an inability to return to sleep (also called late insomnia)

b. The sleep disturbance causes clinical significant distress or impairment in one or more important areas of function in life.
c. The sleep difficulty occurs at least 3 nights of the week.
d. The sleep difficulty is present for at least 3 months.
e. Occurs despite the opportunity for adequate sleep
f. The insomnia is not better explained by another sleep-wake disorder or comorbid mental or physical condition and is not attributable to the effects of a substance.
g. Evaluation of insomnia should include an assessment of medical and psychiatric status. Medical causes are many and include disorders of the heart and lungs, disorders of the musculoskeletal system, diabetes, thyroid disease, and therapy with medications that can interfere with sleep. A detailed sleep history should be obtained that should include an evaluation of nighttime sleep, daytime functioning, sleep-wake rhythms, the sleeping environment, beliefs about sleep, and development of the sleep problem.

6. Parameters used to monitor sleep
   a. Sleep onset latency (SOL): Time that it takes to transition from wakefulness to sleep
   b. Total sleep time (TST): Total sleep period (time in bed) minus the time spent awake
   c. Wake time after sleep onset (WASO): Time spent awake after initial sleep onset until awakening
   d. Sleep efficiency: Ratio of TST divided by the time spent in bed; reported as a percentage
7. Treatment goals
   a. Primary
      i. Improved sleep quality and time
      ii. Improved insomnia-related daytime impairments
   b. Other goals:
      i. SOL less than 30 minutes
      ii. WASO less than 30 minutes
      iii. Decreased frequency of awakenings
      iv. TST greater than 6 hours
      v. Sleep efficiency greater than 80%–85%
      vi. Formation of positive and clear association between the bed and sleeping
      vii. Improvement in sleep-related psychological distress
8. Nonpharmacologic management of insomnia
   a. CBT for insomnia (CBT-I) is considered the gold standard of therapy and is first line in many insomnia guidelines. CBT-I combines cognitive therapy with behavioral treatments, such as stimulus control and sleep restrictions, with or without relaxation therapy. For insomnia, the cognitive therapy portions work with the patient to identify maladaptive behaviors and cognitions that contribute to the patient's insomnia, bring the associated cognitive distortions to the patient's attention, and work with the patient to structure the thoughts into more sleep-compatible forms. CBT-I requires a trained professional and thus may not be available to all patients.
   b. Stimulus control is designed to extinguish the negative associations between the bed and undesired outcomes. The objective is to form a positive relationship between the bed and sleep and to foster a stable sleep-wake schedule. It involves the following:
      i. Go to bed only when sleepy.
      ii. Maintain a regular sleep schedule.
      iii. Avoid naps.

iv. Use the bed only for sleep or sexual activity.
v. If unable to fall asleep (or back to sleep) within 20 minutes (perceived, not by watching the clock), get out of bed, engage in a relaxing activity until drowsy, and then return to bed; repeat as necessary

c. For all types of insomnia, patients can be instructed about good sleep hygiene in conjunction with stimulus control. These principles include:
i. Maintain regular bedtimes and awakenings.
ii. Sleep long enough to avoid feeling tired, but no more.
iii. Optimize the bedroom conditions (e.g., light, temperature, minimize noise or use white noise).
iv. Exercise regularly early in the day, but avoid vigorous exercise in the evening.
v. Develop a bedtime ritual (at least 30 minutes) that allows you to unwind.
vi. Have a light snack or beverage before bed, if hungry, but avoid heavy meals or spicy food.
vii. Avoid stimulants such as caffeine and nicotine throughout the day, but particularly in the afternoons and evenings.
viii. Avoid alcohol because it can lead to "fragmented" sleep.
xi. Cover the clock or phone to minimize the risk of focusing on it throughout the night.
x. Disconnect electronics and avoid light-emitting devices (e.g., television, phones, tablets, and computers) for at least 5–10 minutes before bed.
xi. Ensure adequate exposure to natural light during the day.

C. Pharmacotherapy of Insomnia
1. Pharmacotherapy works best for insomnia when it is part of an overall plan to deal with the causes and is used for well-defined periods. Initial treatment for 2–4 weeks may be appropriate, with a reevaluation of the continued need for treatment. Some patients with chronic insomnia may be appropriate candidates for longer therapy durations, though evidence for long-term use of medications is sparse. Little empiric evidence exists to guide treatment. If hypnotic medications are used long term, regular follow-ups should be scheduled at least every 6 months to monitor use. If a hypnotic is used long term, it should be tapered, not discontinued abruptly. Guidance for deprescribing hypnotics can be found at https://deprescribing.org/.
2. Agents that can depress respiration should be avoided in patients with respiratory disorders, a history of SUD, or obstructive sleep apnea.
3. In the past, barbiturates were used as hypnotics. They are no longer indicated because of the risk of respiratory depression, with no respiratory depression ceiling.
4. Benzodiazepines
a. In general, they are safe, effective, and well tolerated by most patients, but they are not considered first line. Although all members of this class can be used as sedatives, only five are FDA approved and marketed as such. These five are primarily used as sedative-hypnotics because they are rapidly absorbed and produce CNS actions more quickly than most anxiety agents. Table 14 lists the sedative-hypnotic benzodiazepines. They are primarily differentiated by their onset of action and half-life in the body. According to their half-life, they are classified as short acting (half-life less than 6 hours), intermediate acting (half-life 6–24 hours), and long acting (half-life more than 24 hours). These are important parameters when selecting therapy. For instance, someone with problems falling asleep would probably benefit from an agent with a quick onset but short duration of action. Someone with problems maintaining sleep in the middle of the night might respond better to a drug with a longer half-life.

Table 14. Benzodiazepines for Insomnia

Drug (trade)	Usual Dose (mg)	Half-Life (hr)	Duration
Triazolam (Halcion)	0.125–0.25	2–6	Short
Temazepam (Restoril)	15–30	8–20	Intermediate
Estazolam (Prosom)	1–2	8–24	Intermediate
Flurazepam (Dalmane)	15–30	48–120	Long
Quazepam (Doral)	7.5–15	48–120	Long

b. Benzodiazepines are usually well tolerated. However, several problems still exist.
   i. Tolerance: Tolerance can develop, particularly when the drugs are used consistently for long periods. These drugs are not indicated for chronic use; however, newer evidence is emerging that they may be effective for longer periods than originally thought. Most are effective for 2–4 weeks and, in some cases, longer. An intermittent pattern of use can reduce the development of tolerance. In addition, most people without a history of SUD do not escalate their doses.
   ii. Residual daytime sedation: This is a common concern of patients using these drugs and is especially likely with agents having a long half-life. Dose is also an important factor; always use the lowest effective dose.
   iii. Rebound insomnia: This can occur when the drug is discontinued abruptly. Insomnia is usually worse than at baseline and usually lasts for 1–2 days; tapering the drug may minimize its effect. Insomnia is most common after the use of short- and intermediate-acting agents.
   iv. Anterograde amnesia: All benzodiazepines appear to impair the acquisition and encoding of new information. They may also impair memory storage and recall. Incidence may be dose-dependent.
   v. Special populations: Be careful when using benzodiazepines in older adult patients because benzodiazepines can cause memory problems, increase the risk of falls, and accumulate (agents with a long half-life). If a benzodiazepine is used in this population, temazepam is preferred because of its phase II metabolism. Idiosyncratic reactions can occur in older adult and pediatric populations with benzodiazepine use.
   vi. Withdrawal: Physical dependence will occur if these agents are used for more than 2–4 weeks. Symptoms of withdrawal include worsening insomnia, anxiety, muscle twitches, photophobia, tinnitus, auditory and visual hypersensitivity, and seizures. Minimize by gradually tapering the drug at discontinuation. Guidelines for deprescribing benzodiazepine and benzodiazepine receptor agonists in patients with insomnia are available (Can Fam Physician 2018;64:339; see also https://deprescribing.org/), which recommend a slow taper.

D. Nonbenzodiazepine Receptor Agonists (Z-drugs)
   1. Eszopiclone (Lunesta): This nonbenzodiazepine is a $GABA_A$ agonist whose half-life is 6 hours; thus, morning effects can result if it is taken late in the night. Eszopiclone can be used for chronic insomnia. The FDA reduced the starting dose to 1 mg to minimize next-day impairment. Patients should be counseled to use caution when driving or performing activities that require alertness, particularly with the 2- to 3-mg doses. Eszopiclone should be taken immediately before bed and when the patient will be in bed for at least 7–8 hours. Eszopiclone can cause a metallic taste in the mouth.
   2. Zaleplon (Sonata): This is a nonbenzodiazepine with a pharmacology similar to zolpidem (see the text that follows) and a very short half-life. For patients with sleep maintenance problems, it may not last as long. However, zaleplon has a shorter half-life (about 1 hour) and may cause fewer problems in the morning, especially if given late. Zaleplon shortens onset to sleep but does not prolong sleep time or number of awakenings. Zaleplon is indicated only for short-term treatment of insomnia and has been used in trials for up to 5 weeks.

3. Zolpidem (Ambien): This nonbenzodiazepine sedative-hypnotic modulates the $GABA_A$ receptor complex.
   a. Compared with benzodiazepines, zolpidem lacks anticonvulsant action, muscle-relaxant properties, and respiratory depressant effect; it also has a lower risk of tolerance and withdrawal. Zolpidem should still be avoided in obstructive sleep apnea. Zolpidem is a good choice for patients in whom benzodiazepines should be avoided.
   b. Zolpidem is available as an IR tablet, CR tablet (Ambien CR), sublingual tablet (Edluar, Intermezzo), and sublingual spray (Zolpimist). The pharmacokinetics and indications vary depending on the dosing form. The sublingual spray has a shorter onset of action, but that of the sublingual tablet is similar to both the IR and the CR tablets.
   c. Indications vary by dosage form. All are indicated to decrease sleep latency. The CR tablets are indicated to improve sleep maintenance and can be used for longer-term therapy. The sublingual tablet formulation Intermezzo, but not Edluar, is indicated as an "as-needed" treatment for patients who have difficulty falling back to sleep as long as 4 hours or more remain.
   d. The FDA has reduced the dosing recommendations to limit next-day impairment. Dosing differs on the basis of the patient's sex and degree of debility. For women, the nightly dose is 5 mg (IR) or 6.25 mg (CR). For men, it is 5–10 mg (IR) or 6.25–12.5 mg (CR). Debilitated patients should receive 5 mg (IR) or 6.25 mg (CR). Patients should be maintained on the lowest dose needed to benefit.
4. Patients should be warned about the potential risk of engaging in complex behaviors while asleep when taking sedative-hypnotics. Such behaviors may include driving, eating, having sex, or talking on the telephone while asleep (with amnesia for the event). Other cautions include anaphylaxis and decreased respiratory drive.

Table 15. Nonbenzodiazepines for Insomnia

Drug	Half-Life (hr)	Administration (minutes before sleep)	Indications			DEA Scheduling
			Sleep Onset	Sleep Maintenance	Chronic Therapy	
Doxepin (Silenor)	Doxepin: 15.3 Nordoxepin: 31	30		X		Not controlled
Eszopiclone (Lunesta)	6	Immediately	X	X	X	C-IV
Lemborexant (Dayvigo)	17–19 (dose-dependent)	Immediately	X	X		C-IV
Ramelteon (Rozerem)	1–2.6	30	X		X	Not controlled
Suvorexant (Belsomra)	12	30	X	X		C-IV
Zaleplon (Sonata)	1	Immediately	X			C-IV
Zolpidem (Ambien)	1.4–6.5	Immediately	X	X (CR only)	X (CR only)	C-IV

DEA = Drug Enforcement Administration.

E. Orexin (OX1 and OX2) Receptor Antagonists
   1. The neuropeptide orexin promotes wakefulness. By blocking the OX1R and OX2R receptors, both lemborexant (Dayvigo) and suvorexant (Belsomra) decrease sleep latency and promote sleep maintenance. Orexin receptor antagonists are contraindicated in patients with concomitant narcolepsy.

2. Lemborexant is the newest hypnotic. It should be taken with at least 7 hours of remaining sleep. It is metabolized by 3A4, and use should be avoided in patients taking either inducers or inhibitors of 3A4. Time to onset may be delayed if taken with food.
3. Suvorexant should be taken within 30 minutes of bedtime and with at least 7 hours of sleep time. Suvorexant is metabolized by 3A4, and the dose must be decreased in patients taking concomitant 3A4 inhibitors.

F. Miscellaneous Agents
1. Doxepin (Silenor) is a TCA indicated for impaired sleep maintenance. Doses used are lower than for depression. Chances for morning effects are high because of the long half-life of both doxepin and its active metabolite, nordoxepin.
2. Ramelteon (Rozerem): Melatonin agonist (no activity at the GABA or benzodiazepine receptor). Duration is 2–5 hours. To date, there is no evidence that this melatonin agonist is associated with dependence or tolerance, and it can be used long term for chronic insomnia. Ramelteon is primarily metabolized by 1A2, but inducers and inhibitors of 2C9 and 3A4 can also affect it. Ramelteon should be avoided in patients with severe sleep apnea.
3. Taking any of the agents listed in Table 15 with food can delay onset of effects, thus prolonging the time to onset of sleep and increasing the risk of hangover effects in longer-acting agents. Doxepin should be separated from meals by 3 hours.
4. Over-the-counter medications: These are most often antihistamines (doxylamine or diphenhydramine) that are both sedating and anticholinergic. They are possibly effective, but not as effective as benzodiazepines. Regular use is not recommended. In fact, some data suggest that they do not maintain efficacy beyond a few days. They are associated with a higher incidence of daytime sedation than short- or intermediate-acting benzodiazepines. Diphenhydramine has been popular when benzodiazepines were contraindicated. However, caution should be used in older adult patients because an anticholinergic action can cause delirium or worsen dementia or other medical conditions. In addition, diphenhydramine should not be administered with the cholinesterase inhibitors used for Alzheimer disease.
5. Other: In some situations, antidepressants such as trazodone can be used as sedative-hypnotics. These can be effective, and often, the dose required is lower than for depression. However, efficacy has not been fully established through clinical trials. Trazodone has been popular for managing insomnia caused by SSRI antidepressants (see discussion in Depression section). Trazodone is also popular by itself as a sleep agent because the potential for dependence is low. However, trazodone is associated with considerable adverse effects, and the data for long-term use are scant.

G. Guideline-Based Treatment (Chronic Insomnia)
1. American Academy of Sleep Medicine (J Clin Sleep Med 2017;13:307-49)
   a. Initial (sleep onset) insomnia: Zaleplon, triazolam, ramelteon
   b. Middle (sleep maintenance) insomnia: Suvorexant, doxepin
   c. Sleep onset and maintenance insomnia: Eszopiclone, zolpidem, temazepam
   d. Recommends against: Trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, valerian
   e. Inadequate data for other agents
2. American College of Physicians (Ann Intern Med 2016;165:125-33)
   a. General population: Eszopiclone, zolpidem, suvorexant, doxepin
   b. Older adults: Eszopiclone, zolpidem, ramelteon, doxepin
3. VA/DoD (available at https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp)
   a. Recommended: Doxepin, nonbenzodiazepine receptor agonist
   b. Insufficient evidence: Ramelteon, suvorexant
   c. Recommend against: Antipsychotics, benzodiazepines, chamomile, diphenhydramine, kava kava, melatonin, trazodone, valerian

Patient Cases

Questions 20–22 pertain to the following case.

A 50-year-old patient with a 25-year history of alcohol dependence was found unconscious after his last drinking binge. He was first admitted to the medical unit for alcohol withdrawal symptoms before being transferred to the substance dependence unit. His last drink was 6 hours ago, and fluids have been initiated. He has had three alcohol withdrawal seizures in the past and an episode of delirium tremens. He also has significant hepatitis, and liver function tests show AST 275 U/L and ALT 130 U/L. Additional laboratory test values include albumin 4.2 g/dL, alkaline phosphatase 152 IU/L, and γ-glutamyl transferase 470 units/L.

20. Which symptom are you most likely to observe in the medical unit in this patient?
    A. Alcohol craving.
    B. Delirium tremens.
    C. Increased heart rate.
    D. Seizures.

21. Which agent is best for his alcohol withdrawal symptoms?
    A. Chlordiazepoxide.
    B. Clonazepam.
    C. Diazepam.
    D. Lorazepam.

22. Which medication is best for his alcohol dependence?
    A. Acamprosate.
    B. Diazepam.
    C. Disulfiram.
    D. Naltrexone.

23. A 34-year-old man wants to stop using oxycodone. He has been buying it off the street and is using 160 mg daily. He is not interested in methadone maintenance. He would like to enroll in an outpatient program. He is 24 hours after his last dose. He is having some anxiety and muscle aches. He will start his treatment in the clinic. Which is the best formulation and dose to initiate in this patient?
    A. Buprenorphine 2 mg.
    B. Buprenorphine 4 mg.
    C. Buprenorphine/naloxone 2/1.
    D. Buprenorphine/naloxone 4/1.

VI. SUBSTANCE USE DISORDER

A. *DSM-5* Criteria
   1. The DSM-5 recognizes a range of SUDs. Pharmacologic therapy is available for alcohol, opioid, and tobacco use disorders.
   2. General criteria for SUD: A pattern of use leading to clinically significant impartment or distress, as manifested by at least two of the following, occurring within a 12-month period:
      a. More of the substance is taken or the substance is taken longer than intended
      b. There is persistent desire or unsuccessful efforts to cut back or control use
      c. Much time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
      d. Craving, or a strong desire or urge to use
      e. Recurrent use resulting in a failure to fulfill major obligations, such as at work, school, or home
      f. Continued use despite persistent or recurrent social or interpersonal problems caused by or exacerbated by the substance
      g. Because of substance use, the individual gives up or reduces important social, occupational, or recreational activities
      h. Recurrent use in situations in which it is physically hazardous
      i. Continued use despite knowledge of having a continued physical or psychological problem that is caused or exacerbated by use of the substance
      j. Tolerance, as evidenced by a need for more of the substance for the desired effect
      k. Withdrawal symptoms after a decrease in or discontinuation of use

B. Screening for SUD
   1. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), all health care providers should screen for alcohol, tobacco, and other substance misuse (including opioids). Many validated tools exist for this purpose. A good review can be found in SAMHSA at https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP20-02-01-006.
   2. SBIRT model: Screening, brief intervention, and referral to treatment
      a. SBIRT is an evidence-based and universal approach to screening for SUD that is endorsed by SAMHSA. More information can be found at https://www.samhsa.gov/sbirt/about.
      b. SBIRT steps:
         i. Screening: Quickly assesses the severity of substance use and identifies the appropriate level of treatment
         ii. Brief intervention: Focuses on increasing insight and awareness regarding substance use and motivation toward behavior change
         iii. Referral to treatment: Those identified as needing more extensive treatment are provided with the appropriate access to specialty care.

C. SUDs are often comorbid with other psychiatric diagnoses.

D. Withdrawal from use of most substances of abuse is not life threatening, but can be distinctly uncomfortable. The exceptions to this are withdrawal from alcohol, benzodiazepines, and barbiturates, which are life threatening and should be undertaken with medical supervision.

E. Goal: Remission of the disorder, leading toward lasting recovery

F. Addiction (or SUD) is a treatable chronic illness.

G. Treatment of SUD should be patient centered and use shared decision-making, motivational interviewing, and harm reduction strategies, as appropriate.

H. Alcohol
   1. CAGE questionnaire (for screening for alcohol use disorder)
      a. Questions:
         i. Have you ever felt you should **Cut** down on your drinking?
         ii. Have people **Annoyed** you by criticizing your drinking?
         iii. Have you ever felt bad or **Guilty** about your drinking?
         iv. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**Eye-Opener**)?
      b. Scoring: 0 for each "no," 1 for each "yes." A score of 2 or more is a positive screen for problematic drinking. A score of 1 or more suggests the need for follow-up.
   2. Acute withdrawal
      a. Characteristic symptoms occur after alcohol discontinuation. The symptoms that develop, how quickly they develop, and the degree of severity depend on the level of alcohol use and a person's characteristics. Not all patients develop delirium tremens, nor do all develop seizures. These symptoms are difficult to predict, so detoxification should always be supervised. A history of alcohol withdrawal complications suggests that inpatient detoxification is indicated.
      b. Table 16 lists the stages of acute alcohol withdrawal.

Table 16. Stages of Acute Alcohol Withdrawal

Stage	Onset (after last drink or decrease in intake)	Symptoms
1	6–12 hr	Minor withdrawal symptoms: Agitation, anorexia, anxiety, diaphoresis, headaches, insomnia, nausea/vomiting, tachycardia, tremors
2	12–24 hr	Alcohol hallucinosis: Hallucinations – usually visual, but can be auditory or tactile (usually resolve within 48 hr)
3	24–48 hr	Withdrawal seizures (generalized tonic-clonic)
4	48–72 hr (peaks at 3–5 days)	Delirium tremens (alcohol withdrawal delirium): Agitation, diaphoresis, disorientation, hallucinations (usually visual), hyperpyrexia, hypertension, tremor

      c. Delirium tremens, which can be life threatening, should be considered a potential medical emergency and treated promptly.
      d. The seizures that occur are often difficult to control. Status epilepticus can develop; thus, it is important to ensure these patients have intravenous access before onset.
   3. Treatment of acute alcohol withdrawal
      a. The degree of symptoms and the resulting treatment level should be individualized, and an accurate history regarding amount, duration, and past withdrawal symptoms, including seizures and delirium tremens, should guide treatment.
         i. Because of cross-tolerance at the $GABA_A$ receptors, benzodiazepines are considered first-line treatment for alcohol withdrawal symptoms, including delirium tremens and seizures.
         ii. Chlordiazepoxide, clorazepate, diazepam, and oxazepam carry FDA indications for treating alcohol withdrawal, but other benzodiazepines are used off-label. Long-half-life benzodiazepines such as chlordiazepoxide and diazepam minimize the potential for breakthrough symptoms and allow for more self-taper between doses but may also lead to overmedication,

particularly in older adult patients or patients with liver disease. Lorazepam or oxazepam is preferred in these patients. Lorazepam's shorter half-life allows for tighter control of dosing with minimal risk of oversedation.

iii. Several dosing regimens are used (Table 17). Symptom-driven treatment using the Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) is the gold standard. The CIWA-Ar consists of seven items and has a range of 0–67. The higher the score, the more severe the symptoms. The patient's CIWA-Ar score is determined routinely. Patients are typically treated if the score is greater than 8–10 (depending on facility protocol). This protocol is efficacious and results in lower total benzodiazepine use.

iv. Scheduled dosing: For severe alcohol withdrawal, including in patients with a history of withdrawal seizures or delirium tremens, fixed-dose benzodiazepine therapy is used for 2–3 days, regardless of symptoms, with supplementation according to the CIWA-Ar score. The benzodiazepine can then be tapered for 3–4 days until symptoms have abated. The drawback of using scheduled dosing is the risk of overmedication. It is not appropriate for mild-moderate withdrawal or outpatient treatment.

v. Loading-dose (front loaded) protocol: A new approach during recent years uses a loading-dose strategy for chlordiazepoxide. It is given at a dose of 25–100 mg every 1–2 hours until the withdrawal symptoms are alleviated (or CIWA-Ar is less than 10). Most patients will need two or three doses, especially those with a history of seizures during withdrawal, in which case three doses should be used. The half-life of chlordiazepoxide is long, and most patients will not need subsequent doses in this protocol once symptoms are relieved. Of course, patients should be monitored closely.

Table 17. Benzodiazepines for Acute Alcohol Withdrawal

Drug	CIWA-Ar Dosing	Fixed-Dose Regimen	Comments
Chlordiazepoxide (Librium)	25–100 mg PO/IV	50 mg every 6–12 hr × 4; then 25 mg every 6 hr × 4; then 25 mg BID; then 25 mg at bedtime	Long acting; decrease dose for liver disease
Diazepam (Valium)	5–20 mg PO/IV/IM[a]	10 mg every 6 hr × 4; then 5 mg every 6 hr × 8	Decrease dose for liver disease
Lorazepam (Ativan)	2–4 mg PO/IV/IM	2 mg every 6 hr × 4; then 1 mg every 6 hr × 8	Preferred medication, particularly for older adults and those with liver disease; no active metabolites
Oxazepam (Serax)	10–30 mg PO	30 mg every 6 hr × 4; then 15 mg every 6 hr × 4	Short-acting; preferred in older adults and those with liver disease

[a]IM administration of diazepam is unreliable.

BID = twice daily; IM = intramuscular(ly); IV = intravenous(ly); PO = oral(ly).

b. Nutritional considerations

i. Thiamine: Should be given to all patients to prevent Wernicke-Korsakoff syndrome. Because thiamine has poor oral bioavailability, it is administered intramuscularly/intravenously to replete thiamine in severe cases: 100–250 mg intramuscularly/intravenously daily for 3–5 days, followed by 100 mg by mouth three times daily for 1 week, and then 100 mg daily thereafter. Always give the first dose before glucose because thiamine is a cofactor for the metabolism of glucose.

ii. Magnesium: Assess by serum chemistry; if low, give an intravenous supplement.

iii. Electrolytes: Assess by serum chemistry, and add to intravenous solutions as indicated (e.g., potassium).
iv. Vitamins: Patients are usually undernourished; a multivitamin may be indicated.
v. Fluid therapy: The patient may initially be overhydrated, but usually, fluid deficit will follow; replace fluids, usually with intravenous 5% dextrose solution with half-normal saline plus other electrolytes (e.g., potassium, phosphate).

c. Other agents: Anticonvulsants: as adjuncts to benzodiazepines in uncontrolled seizures. They should not be used as monotherapy for alcohol withdrawal seizures. Carbamazepine, gabapentin, and valproic acid have all been used. Of note, gabapentin does not decrease benzodiazepine requirements as assessed by CIWA-Ar in clinical studies.

4. Medications for alcohol use disorder
   a. Acamprosate (Campral) and naltrexone (Revia, Vivitrol) are considered first line.
   b. Naltrexone: This drug can also be used chronically and reduces cravings. If used, it should be combined with CBT. Naltrexone has a precaution listed for hepatocellular injury. Patients should have liver function tests monitored periodically. Naltrexone should be avoided in patients with acute hepatitis or severe hepatic impairment (liver function tests greater than 3 times the upper limit of normal). Additional adverse effects include nausea, diarrhea, injection site reactions, headache, insomnia, and nervousness. The ER injectable suspension (Vivitrol) is available in an intramuscular formulation and is approved for alcohol dependence in patients who can abstain from alcohol in an outpatient setting before treatment initiation. Naltrexone is also available as a daily oral tablet. For further details on use, see the naltrexone entry under Opioid Use Disorder in the text that follows.
   c. Acamprosate (Campral): This drug is a structural analog of GABA that also reduces cravings. Evidence regarding efficacy is more mixed than with naltrexone. Acamprosate is not metabolized by the liver; however, it must be taken three times daily. The dose must be decreased for a CrCl of 30–50 mL/minute/1.73 m^2, and the drug should not be used in patients with a CrCl less than 30 mL/minute/1.73 m^2. It carries a warning for suicidal ideation and should not be used in patients with active suicidal ideation.
   d. Disulfiram (Antabuse): This drug blocks acetaldehyde dehydrogenase. If alcohol is used with it, acetaldehyde concentrations increase. The person will develop symptoms that include nausea/vomiting, flushing, and headache, among others. For this reason, it is considered aversion therapy. Adherence is critical, and disulfiram is usually reserved for patients with considerable motivation for adherence. Caution should be exercised in patients with liver disease, particularly if it is severe or the patient has cirrhosis. Disulfiram has been associated with hepatotoxicity, though it is not known whether patients with existing liver disease are at an increased risk. Because of the increase in acetaldehyde concentrations, it should be avoided in patients with severe myocardial disease. It should not be combined with metronidazole because of an increased risk of encephalopathy.

I. Opioid Use Disorder (OUD)
   1. Opioid-related overdose deaths, illicit use, and prescription misuse constitute a public health crisis.
   2. Opioid intoxication
      a. Symptoms include miosis (unless mydriasis occurs secondary to anoxia from overdose), together with one of the following signs beginning after opioid use: drowsiness or coma, slurred speech, or impaired attention or memory.
      b. Naloxone should be considered for all patients exposed to opioids regardless of the source. An excellent educational source is available at the College of Psychiatric and Neurologic Pharmacists (CPNP): https://cpnp.org/_sdocs/guideline/naloxone/naloxone-access.pdf. SAMHSA has an Opioid Overdose Prevention Kit available at https://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA18-4742.

3. Opioid withdrawal
    a. Not life threatening in the absence of concomitant medical conditions. See Table 18 for details.

Table 18. Timeline of Physical Signs of Opioid Withdrawal

Stage (after last use)	Grade	Physical Signs/Symptoms
Early withdrawal (symptoms may resemble mild flu)		
Short-acting opioids: 8–24 hr Long-acting opioids: ≥ 36 hr	1	Diaphoresis Insomnia Lacrimation, rhinorrhea, or both Restlessness Yawning
	2	Abdominal pain Arthralgia Mydriasis Muscle twitching Myalgias Piloerection
Fully developed withdrawal		
Short-acting opioids: 24–72 hr Long-acting opioids: 72–96 hr	3	Anorexia or nausea Extreme restlessness Fever Hypertension Tachycardia Tachypnea
	4	Dehydration Diarrhea, vomiting, or both Fetal position Hyperglycemia Hypotension
Total duration: Short-acting opioids: 7–10 days Long-acting opioids: ≥ 14 days		

Adapted from: Substance Abuse and Mental Health Services Administration (SAMHSA). Medications for Opioid Use Disorder for Healthcare and Addiction Professionals, Policymakers, Patients, and Families TIP 63. Rockville, MD: U.S. Department of Health and Human Services, 2020. Available at https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP20-02-01-006.

    b. Several scales can be used to monitor the severity of opioid withdrawal symptoms. One of the most commonly used is the Clinical Opiate Withdrawal Scale (COWS). It consists of 11 items that are scored from 0 (asymptomatic) to 4 or 5 (severely symptomatic). The maximum score is 48. A score of 5–12 is considered mild, whereas a score of greater than 36 is severe.
    c. First-line treatment for severe withdrawal is buprenorphine or methadone (see Methadone and Buprenorphine sections in the text that follows for details).
    d. Lofexidine (Lucemyra) is newly FDA approved for the treatment of opioid withdrawal. Although less effective than methadone or buprenorphine for withdrawal symptoms, it is appropriate for use when neither methadone nor buprenorphine is available for use. It is an α_2-adrenergic agonist that reduces the release of norepinephrine and reduces sympathetic tone. It has higher selectivity for the α_{2A}-receptor and is thus thought to be less antihypertensive than clonidine. Lofexidine is intended to treat symptoms of opioid withdrawal, and not for long-term therapy to reduce the risk of relapses. It can prolong the QTc interval and thus should be avoided or administered with caution in patients receiving methadone.

e. Medications for OUD: Pharmacologic therapies for maintenance treatment of OUD include methadone, naltrexone, and buprenorphine with or without naloxone.
f. Medication is integral, but not mandatory, to recovery for many people with OUD. Medications used to treat OUD are superior to placebo or no medication for reducing illicit use, maintaining treatment retention, and reducing opioid overdose death. OUD medication allows time for the individual to make necessary life changes that correlate with long-term remission and recovery. Although it should be considered for all patients with OUD, the strongest consideration should be made for patients with moderate to severe OUD.
g. Pharmacologic treatment of OUD should be integrated with outpatient and/or residential treatment and facilitated between transitions of care, whether inpatient to outpatient, or from emergency department visit to outpatient follow-up. Patients can benefit from psychotherapy and individualized social supports.

4. Methadone (Dolophine) (C-II)
   a. Has the most extensive evidence base supporting treatment of OUD. It is the most studied and most widely used medication for severe OUD. The World Health Organization considers it an essential medication.
   b. Full agonist with an affinity for the opioid mu-opioid receptor
   c. Black box warnings
      i. Fatal respiratory depression: Methadone has a long half-life and is highly lipophilic and may be released slowly from tissue once it accumulates there. For this reason, respiratory depression can occur after the analgesic effects peak; thus, overdose is a risk, particularly during initiation, conversion from another opioid agonist, or a dose increase. There is also an increased risk of respiratory depression when combined with benzodiazepines or other CNS depressants.
      ii. Prolonged QTc interval and torsades de pointes can occur. The risk is dose related and more common with daily doses greater than 200 mg, though it has been reported with lower doses used to treat OUD. Appropriate monitoring is indicated. Screen for risk factors for a prolonged QTc, and avoid combining with other agents that can prolong the QTc interval. If the QTc exceeds 500 milliseconds, it is recommended to decrease or discontinue the methadone dose, eliminate other risk factors for QTc prolongation (if possible), and consider an alternative medication, such as buprenorphine.
   d. Metabolized by 3A4; dose should be adjusted for inducers and inhibitors
   e. Standard of care for pregnancy, though buprenorphine use is increasing. May be beneficial with fewer adverse effects
   f. According to the Code of Federal Regulations title 32, section 8: Methadone products for the treatment of OUD are only available through federally regulated opioid treatment programs. Methadone is administered as a single liquid daily dose in a supervised outpatient treatment setting. Patients must come to the opioid treatment program to receive their dose. Arrangements can be made for a single take-home dose on days the treatment clinic is closed. Exceptions can be made for inpatient or emergency treatment. These programs must offer other services, including medical, counseling, vocational, and educational.
   g. Urine drug tests do not routinely screen for methadone. Additional specialized testing is required.
5. Buprenorphine (Subutex, Bunavail, Suboxone, Zubsolv, Sublocade) (C-III; with or without naloxone)
   a. Use of buprenorphine came about as a result of the Drug Addiction Treatment Act of 2000 (DATA 2000), which allows qualifying physicians to apply for a waiver to treat opioid addiction outside an opioid treatment program using schedule III, IV, and V medications that are FDA approved for this indication.
   b. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist of the kappa receptor. The mu-opioid receptor binding affinity is higher than that of full-opioid agonists with a lower intrinsic activity. Thus, buprenorphine will displace morphine, methadone, and other opioid drugs

but only gives a fraction of effect that levels out with increasing doses. This ceiling effect may not provide enough craving control if a patient used high doses of opioid. This allows patients enough effect to "feel normal" but minimizes functional impairment. This also makes the drug safer in overdose situations. At high-enough doses, the kappa antagonist properties can precipitate withdrawal.

c. The partial mu-agonist activity makes buprenorphine less likely to cause respiratory depression. Lethal overdoses are possible, particularly in opioid-naive patients or individuals who combined it with other CNS depressants such as benzodiazepines or alcohol.
d. Adding naloxone reduces abuse potential because naloxone is more rapidly inactivated after oral/sublingual absorption than after parenteral administration. Thus, if the medication is used as intended (sublingually), the likelihood of withdrawal symptoms is low as opposed to dissolving and injecting it.
e. Like with methadone, the World Health Organization considers buprenorphine an essential medication.
f. Dosage forms:
    i. Short-acting buprenorphine: Sublingual tablets (Subutex)
    ii. Short-acting buprenorphine/naloxone (4:1 dosing ratios): Buccal film (Bunavail), sublingual film (Suboxone), sublingual tablet (Zubsolv)
    iii. Long-acting buprenorphine formulations: Implantable subdermal device (Probuphine; discontinued as of October 15, 2020) and ER injection (Sublocade)
g. Treatment with buprenorphine involves three phases: induction, stabilization, and maintenance. Buprenorphine/naloxone is preferred for most patients, including those taking short-acting opioids (hydromorphone, oxycodone, heroin). Patients taking long-acting opioids (methadone, long-acting morphine, long-acting oxycodone) should be tapered to methadone 30 mg/day or less or the equivalent and transitioned to buprenorphine first. It is recommended that these patients be changed to the buprenorphine/naloxone combination after no more than 2 days of buprenorphine monotherapy.
    i. They must also be screened for other SUDs and for appropriateness of buprenorphine therapy. Patients should begin buprenorphine when they have clear signs of opioid withdrawal. In these cases, the opioid receptors are not fully occupied, and buprenorphine is less likely to induce withdrawal. If the patient is transitioning from methadone, it may take 24–48 hours after the last methadone dose for opioid withdrawal symptoms to manifest.
    ii. Patients should receive concomitant counseling and nonpharmacologic treatment support during treatment. Part of the DATA 2000 waiver requires that physicians be able to refer the patient to appropriate supportive services. Counseling should consider all psychosocial factors.
    iii. Induction phase: Find the lowest buprenorphine dose that minimizes cravings for opioids but prevents withdrawal symptoms. Induction can occur in an inpatient setting, an outpatient office setting, or at home. Office induction is preferred for several reasons, including ensuring the patient knows how to take the medication, improving the therapeutic alliance, verifying the presence of opioid withdrawal symptoms and the absence of precipitated withdrawal symptoms, ensuring the lack of sedation 1–2 hours after taking the medication, and using the time between doses for patient self-monitoring. The patient is given a 2- to 4-mg dose of buprenorphine or the 2/0.5-4/1 mg dose of buprenorphine/naloxone. If withdrawal symptoms are not relieved or return before the 2-hour period, a repeat dose is given, up to a total dose of 8 mg or 8/2 mg on day 1. The dose established during the induction phase depends on the presence of withdrawal symptoms on subsequent days, to a maximum of 32/8 mg/day. Clinically significant differences are not usually seen with doses greater than 24 mg/day of buprenorphine.

iv. Stabilization phase: Reached when the patient is without withdrawal symptoms, is not experiencing adverse effects of buprenorphine/naloxone, and no longer has uncontrollable symptoms of craving. Toxicology screens can be used to verify the patient is not using opioids. Patients should be seen weekly until stable. Doses can be adjusted in 2/0.5 to 4/1 increments. Most patients are maintained on 16/4 to 24/6 mg/day.
v. Maintenance phase: Once the lowest dose needed to maintain abstinence is reached, buprenorphine/naloxone therapy can be maintained indefinitely. Nonpharmacologic modalities should continue during this time.
vi. Discontinuation: This should be considered only if the patient is psychologically and medically stable, can maintain a drug-free lifestyle, and no longer feels the drug is necessary to remain abstinent. The medication should be tapered slowly to avoid withdrawal symptoms.

h. The ER subcutaneous injection can be used after induction and adjustment to 8–24 mg daily using a transmucosal formulation of buprenorphine. The dosing is 300 mg monthly for the first 2 months, followed by the usual maintenance dose of 100 mg monthly. If patients have suboptimal clinical response to the 100-mg dose, it can be increased to a maximum of 300 mg. The injected liquid forms a solid mass upon contact with body fluids. For this reason, it carries a black box warning for risk of serious harm (including occlusion, local tissue damage, and thromboembolic events, including pulmonary emboli) or death with intravenous administration. Health care facilities and pharmacies that order and dispense it must be certified through the Sublocade REMS program. As part of this program, the subcutaneous liquid product can only be dispensed to a health care provider for administration by a health care provider. It cannot be dispensed directly to a patient.
i. The implant consists of four 1-in. flexible rods that are placed under the skin in the arm. The rods release buprenorphine for up to 6 months, after which they are removed. The implant is indicated for maintenance treatment of opioid dependence in patients who have had prolonged clinical stability on doses of a transmucosal buprenorphine product of no more than 8 mg/day of Subutex, Suboxone, or a generic equivalent.
j. Buprenorphine is metabolized by 3A4. Use caution with other medications that either induce or inhibit 3A4.

6. Naltrexone (ReVia, Vivitrol)
   a. Either the daily tablet or the ER injectable can be used, but the ER injectable is usually preferred because of better adherence.
   b. The ER injectable is part of a REMS education program. Patients must be counseled on the following points:
      i. Risk of increased opioid sensitivity and opioid overdose
      ii. Risk of severe reactions at the injection site
      iii. Risk of liver injury, including liver damage or hepatitis
      iv. Therapeutic effects of opioid medications taken for pain, cough and cold, or diarrhea may not be felt by the patient.
   c. Unlike methadone and buprenorphine, prescription and administration of naltrexone are not restricted by practice setting or prescriber.
   d. As mentioned previously, the patient must be completely off opioids for 7–10 days before naltrexone is administered (14 days if taking methadone or buprenorphine).
   e. If initiated before release from a controlled environment in which the patient has undergone opioid withdrawal, it can help prevent a return to opioid use. Because naltrexone does not provide opioid agonism, it may not be effective in patients experiencing severe cravings. This presents a risk because the patient may try to overcome the antagonism of naltrexone with high-dose opioids, which can lead to overdose and respiratory depression.

J. Tobacco Dependence
   1. Tobacco use is the main cause of preventable morbidity and mortality.
   2. Smoking cessation reduces the risk of several adverse health effects, including reproductive health outcomes, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and cancer. It is also beneficial to those with preexisting cardiovascular disease and COPD.
   3. According to the CDC, 13.7% of adults smoked cigarettes in 2018. Rates of tobacco use have greatly declined over the past decade, and there are now more former smokers than current smokers.
   4. Smoking cessation counseling is not consistently offered and tends to be directed to patients with tobacco-related conditions. Interventions lasting as few as 3 minutes can make a difference. Patient counseling can help encourage patients who are unwilling to quit to reconsider quitting and act on it in the future.
   5. As of January 2015, the Joint Commission requires inpatient psychiatric services to screen for tobacco use (TOB-1), offer or provide treatment for tobacco dependence (TOB-2), and provide or offer treatment for tobacco dependence at discharge (TOB-3).
   6. On average, seven attempts are necessary for a patient to quit successfully.
   7. Willingness to quit should be assessed by the five A's: *ask* about tobacco use, *advise* to quit, *assess* willingness to attempt to quit, *assist* in quit attempt, and *arrange* for follow-up.
   8. Motivational interviewing can help identify barriers to change and help the patient overcome them.
   9. The five R's can increase motivation to quit: relevance, risks, rewards, roadblocks, and repetition.
   10. Quit lines such as 1-800-QUIT-NOW can facilitate attempts.
   11. Seven pharmacologic agents (five nicotine and two non-nicotine) are available to help. They should be used with nonpharmacologic modalities to increase the success of quitting.
   12. A usual pack contains 20 cigarettes.
   13. Nicotine replacement therapy: All forms are equally efficacious. Patients should be advised to stop smoking completely before initiating. Nicotine replacement therapy is available in the following forms:
      a. Patch: For patients who smoke more than 10 cigarettes/day, start with 21 mg/day for 6 weeks (4 weeks if Habitrol), then 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks. For those who smoke 10 cigarettes/day or less, start with 14 mg/day for 6 weeks, then 7 mg/day for 2 weeks. Patches may be used for longer periods, if needed, to improve success. The patch should be changed when awakening every day. If the patch causes sleep disturbances, including disturbing or vivid dreams, it can be removed at bedtime. Rotate sites.
      b. Gum: The gum should be chewed until a "peppery" or flavored taste develops; it should then be "parked" between the cheek and gum to facilitate buccal absorption. The gum should be chewed and parked for 30 minutes or until the flavor is gone. The maximum amount of gum to use is 24 pieces in 24 hours. At least 9 pieces of gum should be used daily to increase the chances of quitting. Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength. Otherwise, the 2-mg dose is used. One piece of gum should be used every 1–2 hours for the first 6 weeks of therapy, followed by 1 piece every 2–4 hours for weeks 7–9, then 1 piece every 4–6 hours for weeks 10–12. Acidic beverages (e.g., coffee, juices, and soft drinks) interfere with buccal absorption and should be avoided at least 15 minutes before using the gum. Adverse effects include soreness, dyspepsia, hiccups, and jaw ache. These are usually mild and can be corrected with changes in chewing technique.
      c. Lozenge: Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength. Otherwise, the 2-mg dose is used. The lozenge should be dissolved in the mouth rather than chewed or swallowed. The frequency of use and tapering are the same as for the gum. Adverse effects are also similar. At least 9 lozenges should be used at the beginning to increase chances of quitting. Only 1 lozenge should be used at one time. No more than 5 lozenges within 6 hours, maximum 20 lozenges/24 hours

d. Inhaler: Available by prescription only. Each cartridge delivers 4 mg of nicotine over 80 inhalations. The recommended dosing is 6–16 cartridges/day. Results are best if the contents of the cartridges are continuously puffed over about 20 minutes. Recommended treatment length is 3 months, with reduction in frequency during the last 6–12 weeks. As with the gum and lozenges, patients should not drink acidic beverages or eat within 15 minutes of using the inhaler. Delivery decreases at less than 40°F, so the inhaler should be kept in an inner pocket in cold weather. The most common adverse effects are sore throat, coughing, and rhinitis. Inhalers should be avoided in patients with reactive airway diseases.
e. Nasal spray: Available by prescription only. The dose is 0.5 mg delivered to each nostril. One or two doses should be used hourly, up to five doses. The 24-hour maximum is 40 doses. At least eight doses should be used at the start of therapy. Each bottle contains 100 doses. Recommended length of therapy is 3–6 months, with tapering. Risk of dependency is higher than with other forms of nicotine replacement. Inhaling, sniffing, and swallowing can increase the risk of nasal irritation and should thus be avoided when using the spray. Nasal irritation can occur in up to 94% of patients. Although nasal irritation can resolve, many patients may have it as long as 8 weeks into therapy. Nasal spray is not recommended for patients with reactive airway diseases or nasal conditions.
f. Nicotine patches can be used with the as-needed dosage forms to increase the chances of quitting.
g. Patients with a history of cardiovascular disease can use nicotine replacement therapies.
h. The treatment of choice in pregnant women is nonpharmacologic. Nicotine is freely transferred to the fetus throughout pregnancy. Use of cigarettes or nicotine gum in the third trimester has been associated with diminished breathing movement in the fetus. The FDA has developed labeling for nicotine replacement products in pregnancy. Although the FDA advises using these products only on the advice of a health care provider, it also states that the products are believed to be safer than smoking.

14. Bupropion SR: Should be initiated 7 days before the quit date. Treatment should last for at least 8 weeks but can be continued for up to 6 months to increase the chances of quitting. Bupropion can also be combined with the nicotine patch, if needed.
15. Varenicline: A nicotine receptor partial agonist. Varenicline blocks the effects of nicotine from smoking. Varenicline should be started 1 week before the quit day, though patients can choose to quit smoking up to 35 days after starting varenicline. Varenicline should be continued for a total of 12 weeks. If the patient is successful at smoking cessation, varenicline can be continued for another 12 weeks. The black box warning about neuropsychiatric symptoms was removed in 2016. A meta-analysis and systematic review showed that the risk of neuropsychiatric symptoms was not significantly different from placebo (BMJ 2015;350:h1109). An FDA advisory warned of a small increase in the risk of cardiovascular events, particularly in patients with preexisting cardiovascular disease. The benefits of smoking cessation must be weighed against the possible risk. Varenicline must be used with caution in patients with a CrCl less than 30 mL/minute/1.73 m^2. Combining varenicline with nicotine replacement therapy may increase adverse effects, though varenicline has been used in combination with the nicotine patch. Varenicline can be combined with bupropion.
16. Other agents used include clonidine and nortriptyline.
17. Patients who were unsuccessful in quitting on one form of pharmacologic therapy should be tried on a different method.

18. The American Thoracic Society has released guidelines for initiating pharmacologic treatment in tobacco-dependent adults. The ATS makes five strong recommendations and two conditional recommendations.
    a. Strong recommendations: For tobacco-dependent adults in whom treatment is being initiated:
        - Varenicline is recommended over a nicotine patch.
        - Varenicline is recommended over bupropion.
        - Varenicline plus a nicotine patch is recommended over varenicline alone.
        - Varenicline is recommended over electronic cigarettes.
        - In patients who are not ready to discontinue tobacco use, it is recommended to start varenicline treatment rather than wait until patients are ready to stop.
    b. Conditional recommendations:
        - For tobacco-dependent adults with comorbid psychiatric conditions in whom treatment is being initiated, varenicline is recommended over a nicotine patch.
        - For tobacco-dependent adults, extended-duration (more than 12 weeks) therapy with varenicline is recommended over standard-duration (6–12 weeks) therapy.

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REFERENCES

Schizophrenia

1. Crismon ML, Smith T, Buckley PF. Chapter 84: Schizophrenia. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020.
2. Keepers GA, Fochtmann LA, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, 3rd ed. Washington, DC: American Psychiatric Association, 2020. Available at https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed February 12, 2021.
3. Remington G, Addington D, Honer W, et al. Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry 2017;62:604-16.

Major Depressive Disorder

1. American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd ed. Washington, DC: APA, 2010. Available at http://psychiatryonline.org/guidelines.aspx. Accessed November 13, 2020. Although dated, this is the APA's current guideline.
2. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: APA, 2013.
3. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60.
4. U.S. Department of Veterans Affairs/Department of Defense (VA/DOD); Management of Major Depressive Disorder Working Group. VA/DOD Clinical Practice Guidelines for the Management of Major Depressive Disorder, 3rd ed. Washington, DC: U.S. Department of Veterans Affairs and Department of Defense, 2016. Available at https://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed February 12, 2021.
5. Vandenberg A. Chapter 85: Major depressive disorder. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020.

Bipolar Disorder

1. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: APA, 2013.
2. Drayton SJ, Fields CS. Chapter 86: Bipolar disorder. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020.
3. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013;170:1249-62.
4. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.

Anxiety and Anxiety-Related Disorders

1. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: APA, 2013.
2. Gardner KN, Bostwick JR, Crouse EL. Chapter 88: Anxiety disorders II: posttraumatic stress disorder and obsessive-compulsive disorder. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020.
3. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014;14 (suppl 1):S1. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4120194/pdf/1471-244X-14-S1-S1.pdf. Accessed November 13, 2020.
4. Melton ST, Kirkwood CK. Chapter 87: Anxiety disorders I: generalized anxiety, panic, and social anxiety disorders. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020.
5. U.S. Department of Veterans Affairs/Department of Defense (VA/DOD); Management of Posttraumatic Stress Disorder Working Group.

VA/DOD Clinical Practice Guidelines for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, 3rd ed. Washington, DC: U.S. Department of Veterans Affairs and Department of Defense, 2017. Available at https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal.pdf. Accessed November 14, 2020.

Insomnia

1. Dopp JM, Philips BG. Chapter 89: Sleep-wake disorders. In: DiPiro JT, Yee GC, Posey LM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020.
2. Mukherjee S, Patel SR, Kales SN, et al. An official American Thoracic Society statement: the importance of healthy sleep. Recommendations and future priorities. Am J Respir Crit Care Med 2015;191:1450-8.
3. Pottie K, Thompson W, Davies S, et al. Deprescribing benzodiazepine receptor agonists. Evidence-based clinical practice guideline. Can Fam Physician 2018;64:339-51.
4. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13:307-49.
5. Sherwood DA, Morin AK. 84: Sleep disorders. In: Zeind CS, Carvalho MG, eds. Applied Therapeutics: The Clinical Use of Drugs, 11th ed. Philadelphia : Wolters Kluwer, 2018.

Substance Use Disorders

1. American Society of Addiction Medicine (ASAM). The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. Rockville, MD: ASAM, 2020. Available at https://www.asam.org/Quality-Science/quality/guideline-on-alcohol-withdrawal-management. Accessed November 14, 2020.
2. Davis CM, Valentino N. Pharmacist Toolkit: Opioid Use Disorder. 2019. College of Psychiatric and Neurologic Pharmacists. Available at https://cpnp.org/guideline/oud/online?view=link-1-1530212066&.pdf. Accessed February 12, 2021.
3. Leone FT, Zhang Y, Evers-Casey S et al. Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020;202:e5-e31.
4. McNicholas L. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction TIP 40. Rockville, MD: U.S. Department of Health and Human Services, 2004.
5. Miller NS. Detoxification and Substance Abuse Treatment. TIP 45. Rockville, MD: U.S. Department of Health and Human Services, 2013.
6. Substance Abuse and Mental Health Services Administration (SAMHSA). Medications for Opioid Use Disorder for Healthcare and Addiction Professionals, Policymakers, Patients, and Families TIP 63. Rockville, MD: U.S. Department of Health and Human Services, 2020. Available at https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP20-02-01-006.
7. Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 1989;84:1353-7.
8. U.S. Department of Health and Human Services (HHS). Smoking Cessation. A Report of the Surgeon General. Rockville, MD: HHS, 2020. Available at https://www.cdc.gov/tobacco/data_statistics/sgr/2020-smoking-cessation/index.html#full-report.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A
This patient is experiencing antipsychotic-induced acute dystonias. Benztropine or another anticholinergic should be given to reverse the EPS (neck stiffness and oculogyric crisis) (Answer A is correct). Dantrolene is used for patients with NMS but does not reverse acute dystonias (Answer B is incorrect). Propranolol is useful for akathisia but not for other types of EPS (Answer D is incorrect). Lorazepam can also be used for acute dystonias, but anticholinergic agents are usually preferred. In addition, this patient has a dual diagnosis of SUD; thus, benzodiazepines should be avoided unless absolutely needed (Answer C is incorrect).

2. Answer: B
Aripiprazole has less risk of EPS than haloperidol/FGAs but still carries a risk of EPS (Answer A is incorrect). Although SGAs such as aripiprazole may help reduce negative symptoms, they rarely eliminate them (Answer C is incorrect). Aripiprazole has no evidence to support its use to treat SUDs (Answer D is incorrect). The best reason to use aripiprazole in this patient is that aripiprazole can be converted to an LAI formulation that can be given monthly (Abilify Maintena) or up to every 8 weeks (Aristada) (Answer B is correct).

3. Answer: C
Among the SGAs, aripiprazole is more likely to cause akathisia, which is a form of EPS that involves a subjective feeling of restlessness and inability to sit still (Answer C is correct). Aripiprazole has a low incidence of sedation (Answer A is incorrect). Anticholinergic effects are minimal with aripiprazole (Answer B is incorrect). Although all antipsychotics can potentially cause QTc prolongation, they rarely cause problems in patients without risk factors (Answer D is incorrect).

4. Answer: D
Ziprasidone would be most appropriate, given the patient's history of dystonia with haloperidol (Answer D is correct). Ziprasidone carries a lower risk of causing EPS than FGAs such as fluphenazine (Answer B is incorrect). Clozapine and olanzapine have low risks of EPS as well, but clozapine is reserved for treatment-resistant cases (Answer A is incorrect). Olanzapine would not be preferred because of the significant metabolic risks it could cause in this young patient. Most of the current guidelines for schizophrenia do not consider olanzapine a first-line agent for a patient with newly diagnosed schizophrenia (Answer C is incorrect).

5. Answer: C
Paroxetine would have the most interaction with this patient's current medications because of its interaction with hydrocodone by inhibiting the 2D6 isoenzyme (Answer C is correct). This would result in a lack of analgesic effects from the opiate. Fluvoxamine is a 1A2 inhibitor that does not interact with thiazides, metformin, or opiates (Answer B is incorrect). Citalopram would have no appreciable effects on any of this patient's medications (Answer A is incorrect). The effect of sertraline, though it may compete with hydromorphone (metabolite of hydrocodone) through 3A4, would be less than that of paroxetine (Answer D is incorrect).

6. Answer: C
Mirtazapine is appropriate because it can improve this patient's insomnia and poor appetite (Answer C is correct). In addition, mirtazapine has no drug-drug interactions with the patient's current medications. Bupropion, fluoxetine, and venlafaxine would worsen her insomnia (Answers A, B, and D are incorrect). Although venlafaxine might help her pain, it could worsen hypertension at doses greater than 150 mg daily (Answer D is incorrect), and bupropion decreases appetite and is also a strong inhibitor of 2D6 (Answer A is incorrect).

7. Answer: B
The citalopram dose should be increased to 40 mg/day because this patient had some initial response to the drug (improvement in insomnia and appetite) but may not have reached the maximum tolerated dose (Answer B is correct). The patient has taken citalopram for only 4 weeks, possibly at a subtherapeutic dose (Answer A is incorrect). Adjunctive therapy with SGAs such as aripiprazole should be reserved for patients who have had partial response to therapeutic doses of antidepressants (e.g., citalopram 40 mg daily for at least 4 weeks) (Answer C is incorrect). Changing SSRIs may also be an option after the maximum tolerated citalopram dose is reached (Answer D is incorrect).

8. Answer: D
The patient still needs an antidepressant, and discontinuing citalopram without an alternative agent at 6 months would be inappropriate (Answer A is incorrect). Bupropion is sometimes added to antidepressants for treatment-emergent sexual dysfunction, with some evidence of efficacy. However, bupropion should be avoided in patients with a history of eating disorders, including bulimia (Answer B is incorrect). Changing to a different SSRI might produce the same adverse effect because the patient's anorgasmia appears to be caused by serotonergic activity (Answer C is incorrect). Vortioxetine is associated with a lower incidence of sexual dysfunction than SSRIs. Trial data analyses show that patients with sexual dysfunction taking SSRIs, including citalopram, can have an improvement in their sexual dysfunction when changed to vortioxetine (Answer D is correct).

9. Answer: D
Lithium should be initiated to treat the current manic phase and prevent future episodes (Answer D is correct). Carbamazepine is effective for maintenance treatment but is considered second or third line for acute mania (Answer A is incorrect). Divalproex is also good for maintenance treatment, but given this patient's active hepatitis C, it would not be a good choice (Answer B is incorrect). Lamotrigine is also effective for maintenance but not for treating the patient's current manic phase (Answer C is incorrect).

10. Answer: B
Coarse tremor may indicate lithium toxicity and will require an immediate evaluation of the patient's lithium concentration (Answer B is correct). Lithium can cause hypothyroidism, severe acne, and weight gain, but these can usually be managed with lifestyle modifications or medications (Answers A, C, and D are incorrect).

11. Answer: B
This patient has lithium toxicity, as evidenced by the lithium concentration (1.9 mEq/L) and the accompanying symptoms of confusion and slurred words. Both lisinopril and ibuprofen can increase lithium concentrations. The patient has taken lisinopril for 2 months; thus, the lithium concentration should be stabilized (Answer C is incorrect). Ibuprofen was started in the past week and is thus the most likely culprit (Answer B is correct). Zolpidem might increase sedation, but it should not result in the current symptoms (Answer D is incorrect). The sodium in the oral rehydration solution would be expected to decrease, not increase, the lithium concentrations (Answer A is incorrect).

12. Answer: C
This patient is experiencing a depressive phase of bipolar disorder. Divalproex sodium is more efficacious for manic or mixed episodes and should also be avoided in women of childbearing age, if possible (Answer A is incorrect). Lamotrigine is used for the depressive phase, but it must be titrated slowly to avoid rash. Thus, lamotrigine is not the best choice for an acute episode (Answer B is incorrect). An SNRI such as venlafaxine might increase the risk of switching to mania (Answer D is incorrect). Quetiapine is used for depression associated with bipolar disorder and might also help her sleep at night and improve her appetite (Answer C is correct).

13. Answer: A
Paroxetine should be continued at this time because the patient is successfully being treated for depression, and paroxetine is considered first line for PTSD (Answer A is correct). Sertraline also treats PTSD, but there is no reason to discontinue paroxetine (Answer B is incorrect). Adding adjunctive agents such as lorazepam and buspirone is not indicated because paroxetine was initiated only 3 weeks ago (Answers C and D are incorrect).

14. Answer: C
Both SSRIs and SNRIs are considered first line for GAD and are associated with symptom remission (Answer C is correct). Although benzodiazepines such as alprazolam can relieve symptoms, they are only recommended for short-term treatment (Answer A is incorrect). Although buspirone is effective for GAD, it is not considered first line (Answer B is incorrect). Pregabalin is effective for GAD, but its use is off-label, and it is usually reserved for patients who do not respond to, or cannot tolerate, antidepressants (Answer D is incorrect).

15. Answer: A
Although antidepressants such as paroxetine and venlafaxine are the cornerstones for treating panic disorder, they take time to work and can worsen symptoms

when first initiated (Answers C and D are incorrect). Benzodiazepines effectively treat the acute symptoms of panic disorder and are indicated when panic attacks significantly affect a patient's ability to function in everyday life, such as attending a job (Answer A is correct). Ideally, an antidepressant should be initiated with the benzodiazepine, and the benzodiazepine should later be withdrawn once the patient's condition is stable on the antidepressant. Buspirone is not effective for panic disorder (Answer B is incorrect).

16. Answer: C
Serotonergic activity is necessary for efficacy against OCD. First-line agents include selected SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and clomipramine (Answer C is correct). Desipramine is a secondary amine TCA and has no significant serotonergic activity (Answer B is incorrect). Bupropion has no serotonergic activity (Answer A is incorrect). Mirtazapine does not currently have strong evidence for efficacy in the treatment of OCD (Answer D is incorrect). For these reasons, only clomipramine would be a viable option for treatment.

17. Answer: D
The patient takes levothyroxine at night, which is probably contributing to her insomnia (Answer D is correct). Hydrochlorothiazide and ibuprofen are not significantly associated with causing insomnia (Answers B and C are incorrect). Citalopram may contribute to insomnia in certain patients, but this patient takes it in the morning, which decreases the risk (Answer A is incorrect).

18. Answer: A
The patient does not want a drug with significant daytime sedation, but she needs a drug that will help her stay asleep throughout the night. Eszopiclone is the best option (Answer A is correct). Trazodone has a long half-life that will help her stay asleep but has fewer efficacy data for insomnia (Answer B is incorrect). Temazepam causes daytime sedation (Answer C is incorrect). Zaleplon does not cause daytime sedation, but its short half-life would not help her stay asleep (Answer D is incorrect).

19. Answer: C
Zolpidem and other sedative-hypnotics have been associated with abnormal behaviors such as eating, driving, having sex, and talking on the telephone while asleep (Answer C is correct). Zolpidem may cause orthostasis and disorientation but, when taken appropriately, does not cause significant problems (Answers A and B are incorrect). Zolpidem at high doses has been associated with seizures, but this patient has no history of drug abuse or of using high doses of medications (Answer D is incorrect).

20. Answer: C
The initial symptoms of alcohol withdrawal include hemodynamic instability such as increased heart rate and blood pressure (Answer C is correct). Alcohol craving, delirium tremens, and seizures generally occur after 12 hours of abstinence (Answers A, B, and D, respectively, are incorrect).

21. Answer: D
Lorazepam is appropriate because of the patient's liver abnormalities (Answer D is correct). Lorazepam undergoes glucuronidation and does not rely on oxidative pathways for metabolism. Chlordiazepoxide and diazepam should be avoided in patients with liver disease because of the presence of active metabolites with long half-lives (Answers A and C are incorrect). Clonazepam is generally not used for alcohol withdrawal (Answer B is incorrect).

22. Answer: A
Given the patient's liver disease, acamprosate is most appropriate because it does not rely on hepatic metabolism (Answer A is correct). Disulfiram is not generally recommended in patients with liver disease (Answer C is incorrect). Naltrexone is not indicated in patients with liver function tests greater than 3 times the upper limit of normal (Answer D is incorrect). Diazepam is not used for alcohol dependence but is used during alcohol withdrawal (Answer B is incorrect).

23. Answer: D
For opioid detoxification in the outpatient setting, the combination buprenorphine/naloxone product is preferred (Answers A and B are incorrect). The correct initial dose is 4/1 (Answer D is correct; Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

The patient's symptoms most closely resemble akathisia. The treatment of choice in this case is a lipophilic β-blocker such as propranolol (Answer D is correct). Benztropine is an anticholinergic agent that can be used for other movement disorders such as dystonias or parkinsonian symptoms, but it is not effective for akathisia (Answer A is incorrect). Benzodiazepines are effective for akathisia, but they are not the best choice, given this patient's history of alcohol use disorder (Answer C is incorrect). Dantrolene, a skeletal muscle relaxant, is used for NMS (Answer B is incorrect).

2. Answer: D

This patient has tardive dyskinesia, which involves abnormal, repetitive, involuntary movements. Involvement of the facial muscles, including the jaw, is common. Until recently, very little treatment was available for tardive dyskinesia. In patients with new-onset, mild tardive dyskinesia, discontinuing the suspected antipsychotic or changing to an agent with less likelihood of causing tardive dyskinesia was an option. Of the antipsychotics, clozapine is considered least likely to cause tardive dyskinesia and is thus an agent of choice in patients who develop tardive dyskinesia. Clozapine is also the agent of choice in patients who do not respond to at least two trials of other antipsychotics, including both FGAs and SGAs. This patient's condition is stable on her current regimen (perphenazine), but she not responded to or has not tolerated several other antipsychotics. She also developed diabetes while taking olanzapine, which is closely related to clozapine. For this reason, changing to clozapine would not be best (Answer C is incorrect). Treatments for other forms of EPS, including benztropine and lorazepam, are ineffective for tardive dyskinesias (Answers A and B are incorrect). On April 11, 2017, the FDA approved valbenazine for the treatment of tardive dyskinesia. In a systematic review of its effects, valbenazine had a number needed to treat of 4 to reduce the Abnormal Involuntary Movement Scale by 50% or more, with a number needed to harm (somnolence) of 15. In this patient, who is responding well to her current antipsychotic treatment, valbenazine would be the best choice (Answer D is correct).

3. Answer: B

Clozapine is metabolized by 1A2, an enzyme that is induced by smoking. Smoking cessation can reverse this induction and cause supratherapeutic concentrations of clozapine, resulting in dose-dependent seizures (Answer B is correct). Although bupropion can also cause seizures, the patient has been stable on this dose for 1 month (Answer A is incorrect). Neither diphenhydramine nor metformin is associated with drug-induced seizures at the current doses (Answers C and D are incorrect).

4. Answer: B

Of the agents listed, mirtazapine and the SSRIs fluoxetine and paroxetine are considered first line. Fluoxetine's adverse effect profile most closely counteracts the patient's symptoms. She also has anxiety, and fluoxetine could concomitantly relieve her symptoms of anxiety and allow her to discontinue the benzodiazepine (Answer B is correct). Paroxetine can increase appetite and cause somnolence (Answer D is incorrect), as can mirtazapine (Answer C is incorrect). Although her suicidal ideation is intermittent and passive, desipramine can be fatal in an overdose situation (Answer A is incorrect).

5. Answer: B

Duloxetine is the best choice because it is also indicated for diabetic neuropathy (Answer B is correct). Although nortriptyline is effective for neuropathy, it is not a good choice in a patient with cardiovascular disease. Nortriptyline can also cause weight gain (Answer C is incorrect). Although bupropion is either weight neutral or can lead to some weight loss, data are not strong for its use in neuropathy (Answer A is incorrect). Sertraline would be safe in this patient and could be used as an alternative to citalopram, but it is not effective for neuropathy (Answer D is incorrect).

6. Answer: D

This patient has serotonin syndrome (myoclonus, agitation, diaphoresis). The symptoms are probably caused by adding dextromethorphan to paroxetine. In addition to the serotonergic activity of both agents, paroxetine inhibits 2D6, which is responsible for metabolizing dextromethorphan. This further increases the serotonergic

activity (Answer D is correct). None of the other choices is a combination of serotonergic agents, nor do they interact in a fashion that would increase serotonergic activity (Answers A–C are incorrect).

7. Answer: C

This patient is having an acute depressive episode. He has taken lithium for 5 years, which is long enough to derive any antidepressant effects. His lithium concentration is also within therapeutic range. Quetiapine is FDA indicated for depression associated with bipolar disorder (Answer C is correct). Lithium's onset of action is more rapid than that of lamotrigine, which requires a slow titration to reach therapeutic doses (Answer B is incorrect). Unlike data for aripiprazole in unipolar depression, data analyses for aripiprazole suggest it is not effective for bipolar depression (Answer A is incorrect). The efficacy of antidepressants in treating type I bipolar disorder is questionable, and treatment with an SNRI could lead to a switch to mania (Answer D is incorrect).

8. Answer: D

This patient has hypothyroidism, as indicated by her increased TSH concentrations. Her hypothyroidism was probably induced by lithium (Answer D is correct). Her glucose is likely elevated secondary to her lithium-induced hypothyroidism and is not directly related to lithium therapy (Answer A is incorrect). Even though lithium can "look like" sodium to the body, lithium does not commonly affect sodium concentrations. This patient's sodium concentrations are within the normal range (Answer C is incorrect). Although lithium can impair renal function, this patient's serum creatinine concentration is within the normal range (Answer B is incorrect).

9. Answer: B

This patient's presentation and laboratory results are consistent with acute pancreatitis. Although the incidence of pancreatitis is rare, divalproex can cause this condition. Patients who develop pancreatitis while taking divalproex that resolves when the patient is no longer taking the agent should not be rechallenged (Answer B is correct). Neither aripiprazole nor lamotrigine is associated with pancreatitis (Answers A and C are incorrect). This patient's lamotrigine dose should be lowered to prevent Stevens-Johnson syndrome. Despite lamotrigine's temporal relationship with prednisone, it is probably not contributing to the current clinical picture (Answer D is incorrect).

10. Answer: D

This patient has panic disorder. Benzodiazepines more rapidly treat the acute physical symptoms and fear that occur with panic disorder, but they are not the agents of choice for long-term symptom control (Answer A is incorrect). Selective serotonin reuptake inhibitors such as paroxetine are first line for preventing panic attacks. Although they take time to achieve full efficacy, they are the most effective for maintenance control of symptoms (Answer D is correct). Buspirone is not effective acutely for panic attacks (Answer B is incorrect). Hydroxyzine might offer some sedation, but it would not treat the underlying anxiety disorder (Answer C is incorrect).

11. Answer: C

Although SSRIs and SNRIs are the first-line treatment for GAD, the patient has not responded to several antidepressants. Although it does not carry an FDA indication, pregabalin is also effective against GAD. Several guidelines list it as first- or second-line agent. Pregabalin is similar to antidepressants and benzodiazepines, so it might be a good choice in this patient (Answer C is correct). Venlafaxine has proven efficacy for GAD, but given this patient's lack of response to other antidepressants, it might be suboptimal compared with pregabalin (Answer D is incorrect). Fluoxetine is effective for GAD but is a strong inhibitor of 2D6, which would decrease the efficacy of tamoxifen (Answer B is incorrect). Bupropion is also an inhibitor of 2D6 and is ineffective against most anxiety disorders (Answer A is incorrect).

12. Answer: B

This patient primarily has difficulty with sleep onset and would benefit from an agent that decreases sleep latency and does not prolong sleep. Ramelteon is the only listed agent that produces these effects. Older adults can have difficulty with circadian rhythm, which a melatonin analog may help regulate. Ramelteon is also indicated for chronic insomnia if needed for a prolonged period (Answer B is correct). Although eszopiclone decreases time to sleep, its longer half-life may result in hangover effects (Answer A is incorrect).

Suvorexant also treats sleep maintenance, but it can also cause a hangover effect (Answer C is incorrect). Zolpidem received recent labeling changes for reduced doses and has reduced metabolism in older adults (Answer D is incorrect).

13. Answer: D

To avoid withdrawal symptoms, patients taking long-acting opioids should have doses tapered to the equivalent of methadone 30 mg/day or less before being changed to a buprenorphine regimen (Answer D is correct). Initiating a patient on buprenorphine at higher methadone doses could precipitate withdrawal because of the higher binding affinity of buprenorphine for the mu-opioid receptor with less activity and the added antagonism at the kappa receptor (Answer B is incorrect). Patients taking long-acting opioids such as methadone should be changed to buprenorphine monotherapy before being advanced to buprenorphine/naloxone (Answer A is incorrect). Naltrexone monotherapy is inappropriate because it can precipitate withdrawal (Answer C is incorrect).

14. Answer: A

This patient has alcoholic hepatitis, as indicated by his AST and ALT values. Presumably, these would improve with abstinence. His liver function is intact, as evidenced by his albumin, prothrombin time, and platelet values. Naltrexone might be indicated in this patient, but he is also taking opioids (methadone). Use of naltrexone in patients on methadone maintenance would precipitate withdrawal (Answer D is incorrect), though it could be considered once his liver function tests correct. Disulfiram should be used with caution in patients with active liver disease. Disulfiram also requires a strong commitment on the patient's part to abstain from drinking and may be less effective. This patient has a history of several failed attempts (Answer C is incorrect). Chlordiazepoxide is used during acute alcohol detoxification but plays no role in maintenance therapy (Answer B is incorrect). The acamprosate dose should be reduced to 333 mg orally three times daily for a CrCl of 30–50 mL/minute/1.73 m^2 and is thus the most appropriate choice in this patient (Answer A is correct).

15. Answer: A

This patient's previous quit attempt with nicotine gum was probably unsuccessful because the gum strength (2 mg) and frequency of use (fewer than 9 pieces/day) were too low to manage his nicotine cravings. Thus, his previous use of nicotine gum is not a true treatment failure. He has the two cardinal symptoms suggestive of depression (sad affect and anhedonia), making bupropion a reasonable choice (Answer A is correct). His myocardial infarction is not a contraindication to the use of nicotine products; thus, nicotine gum could be added to bupropion if monotherapy fails (Answers B and C are incorrect). Coronary artery disease is not a contraindication to varenicline therapy, but given this patient's likely concomitant depression, bupropion is a better fit (Answer D is incorrect).

Fluids, Electrolytes, and Nutrition

Leslie A. Hamilton, Pharm.D., FCCP, FCCM, BCPS, BCCCP

University of Tennessee Health Science Center
College of Pharmacy
Knoxville, Tennessee

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Leslie A. Hamilton, Pharm.D., FCCP, FCCM, BCPS, BCCCP

University of Tennessee Health Science Center
College of Pharmacy
Knoxville, Tennessee

Learning Objectives

1. Recommend an appropriate intravenous fluid regimen and monitoring parameters given a patient clinical scenario.
2. Discuss the appropriate roles and risks of hypertonic and hypotonic saline, recommend treatment regimens, and discuss appropriate monitoring parameters to ensure safe and effective use of these intravenous fluids.
3. Assess electrolyte abnormalities and recommend an appropriate pharmacologic treatment plan based on individual patient signs and symptoms.
4. Recommend a patient-specific enteral nutrition (EN) formula, infusion rate, and monitoring parameters based on nutritional needs, comorbidities, and clinical condition.

Abbreviations in This Chapter

AA	amino acid
ADH	antidiuretic hormone
ASPEN	American Society for Parenteral and Enteral Nutrition
BEE	basal energy expenditure
BUN	blood urea nitrogen
D_5W	5% dextrose
EC	extracellular
ECG	electrocardiogram
EN	enteral nutrition
GI	gastrointestinal
IBW	ideal body weight
IC	intracellular
ICU	intensive care unit
IS	interstitial
LBW	lean body weight
MW	molecular weight
NG	nasogastric
PN	parenteral nutrition
SCr	serum creatinine
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
TBF	total body fluid
WBC	white blood cell count

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 74-year-old woman (weight 72 kg) arrives in the emergency department with a 3-day history of cough, body temperature of 102°F (38.9°C), and lethargy. She has the following vital signs and laboratory values: blood pressure 72/40 mm Hg, heart rate 115 beats/minute, urine output 10 mL/hour, white blood cell count (WBC) 18×10^3 cells/mm^3, hemoglobin 12.5 g/dL, and blood urea nitrogen (BUN)/serum creatinine (SCr) ratio of 28:1.7 mg/dL (baseline SCr 1.2 mg/dL), and blood glucose 82 mg/dL. After a 500-mL fluid bolus of 0.9% sodium chloride, her blood pressure is 80/46 mm Hg and her heart rate is 113 beats/minute. Her chest radiograph is consistent with pneumonia. Her medical history includes coronary artery disease and arthritis. Which is the most appropriate treatment at this time?
   A. Furosemide 40 mg intravenously.
   B. 5% albumin 500 mL infused over 4 hours plus norepinephrine titrated to maintain a systolic blood pressure of 90 mm Hg or higher.
   C. 1000-mL fluid bolus with 5% dextrose (D_5W) and 0.9% sodium chloride.
   D. 1000-mL fluid bolus with 0.9% sodium chloride.

2. An order has been received for 2% sodium chloride. Assume no commercially available product is available. Using 0.9% sodium chloride and 23.4% sodium chloride, first determine how much of each is necessary to prepare 1 L of 2% sodium chloride. Second, calculate the osmolarity of 2% sodium chloride. Finally, determine whether the resultant solution should be administered through a central or peripheral intravenous infusion (molecular weight [MW] of sodium chloride is 58.5, osmotic coefficient is 0.93).
   A. Mix 951 mL of 0.9% sodium chloride plus 49 mL of 23.4% sodium chloride; osmolarity = 635 mOsm/L; peripheral intravenous infusion.
   B. Mix 951 mL of 0.9% sodium chloride plus 49 mL of 23.4% sodium chloride; osmolarity = 954 mOsm/L; central intravenous infusion.
   C. Mix 850 mL of 0.9% sodium chloride plus 150 mL of 23.4% sodium chloride; osmolarity = 954 mOsm/L; central intravenous infusion.

D. Mix 850 mL of 0.9% sodium chloride plus 150 mL of 23.4% sodium chloride; osmolarity = 513 mOsm/L; peripheral intravenous infusion.

3. A 68-year-old man is admitted to the hospital for worsening shortness of breath during the past 2 weeks caused by heart failure. His serum sodium concentration on admission was 123 mEq/L. Other abnormal laboratory values include brain natriuretic peptide of 850 pg/mL and SCr of 1.7 mg/dL. Chest radiography is consistent with pulmonary edema. The patient weighs 85 kg on admission, which is up 3 kg from his baseline weight. The patient is not experiencing nausea, headache, or mental status changes. The physician orders 3% sodium chloride to treat the hyponatremia. Which recommendation is best?

   A. 3% sodium chloride is an appropriate choice because the hyponatremia is probably acute.

   B. A 250-mL bolus of 3% sodium chloride is appropriate if used in combination with furosemide to prevent volume overload.

   C. 3% sodium chloride is appropriate as long as the serum sodium does not increase more than 10 mEq/L in 24 hours.

   D. The risks of 3% sodium chloride outweigh the potential benefit for this patient.

4. A 55-year-old man with diabetes and kidney disease has hyperkalemia. His laboratory values include potassium (K^+) 7.2 mEq/L, calcium (Ca^{2+}) 9 mg/dL, albumin 3.5 g/dL, and blood glucose 302 mg/dL. His electrocardiogram (ECG) is abnormal, with peaked T waves. What is the best recommendation for initial treatment?

   A. Regular insulin 10 units intravenously plus 50 g of dextrose intravenously.

   B. 10% calcium gluconate 10 mL intravenously.

   C. Sodium polystyrene sulfonate (Kayexalate) 15 g orally.

   D. Sodium bicarbonate 50 mEq intravenously over 5 minutes.

5. A 68-year-old woman (weight 60 kg) is admitted to the hospital after a cardioembolic stroke. Her medical history is significant for atrial fibrillation, acute myocardial infarction, and diabetes. She has been unconscious for 48 hours. The medical team decides to start feeding the patient. All of her laboratory values, including glucose concentrations, are normal. Although she currently has no enteral access, she does have a peripheral intravenous catheter. Which nutritional regimen is best for this patient?

   A. Insert a central intravenous catheter and initiate parenteral nutrition (PN) containing 60 g of amino acids (AAs), 250 mL of 20% lipid emulsion, 300 g of dextrose, standard electrolytes, multivitamins, and trace elements in a volume of 2000 mL administered over 24 hours.

   B. Insert a central intravenous catheter and initiate PN containing 40 g of AAs, 250 mL of 20% lipid emulsion, 200 g of dextrose, standard electrolytes, multivitamins, and trace elements in a total volume of 2000 mL administered over 24 hours.

   C. Insert a nasogastric (NG) or nasoduodenal feeding tube and infuse an isotonic formula (1 kcal/mL) starting at 25 mL/hour and advance to a goal rate of 65 mL/hour.

   D. Insert a percutaneous endoscopic gastrostomy feeding tube and infuse an isotonic formula (1 kcal/mL) starting at 25 mL/hour and advance to a goal rate of 100 mL/hour.

6. A 70-year-old man is admitted to the hospital with peritonitis caused by severe inflammatory bowel disease. The patient has received adequate fluid resuscitation, and he is prescribed appropriate antibiotics. After several days of the patient being unable to tolerate oral or enteral nutrition, the physician consults the pharmacist to recommend a PN formula to be administered through a central line. The patient is hemodynamically stable, with normal electrolyte concentrations. Weight is 55 kg, BUN/SCr is 20/1.1 mg/dL, and WBC is 17×10^3 cells/mm^3. Assuming that appropriate electrolytes, multivitamins, and trace elements are included, which PN formula, when administered over 24 hours, will best provide this patient adequate calories, AAs, and lipids?

   A. AAs 10% 700 mL, dextrose 30% 325 mL,

lipid 20% 500 mL.

B. AAs 10% 450 mL, dextrose 70% 400 mL, lipid 20% 250 mL.

C. AAs 10% 800 mL, dextrose 70% 350 mL, lipid 20% 250 mL.

D. AAs 15% 900 mL, dextrose 50% 500 mL, lipid 20% 250 mL.

7. A 59-year-old man has been admitted to the hospital after several days of vomiting and diarrhea. In the emergency department, he had several runs of nonsustained ventricular tachycardia. His plasma potassium on admission is 2.8 mEq/L. After 100 mEq of potassium chloride is infused over 24 hours, his repeated K^+ is 3.2 mEq/L, and he continues to have runs of ventricular tachycardia. Other laboratory values include Na^+ 143 mEq/L, magnesium 1.4 mg/dL, phosphorus 3 mg/dL, Ca^{2+} 9 mg/dL, and ionized Ca^{2+} 1.1 mmol/L. Which treatment would be best to give next?

A. Administer potassium chloride 20 mEq intravenously over 1 hour each for 4 doses and recheck K^+.

B. Administer magnesium sulfate as a 2 g slow intravenous infusion over 2 hours.

C. Administer potassium phosphate 15 mmol intravenously over 4 hours.

D. Administer calcium gluconate 2 g intravenously over 5 minutes.

8. Which nutritional strategy can best prevent gut mucosal atrophy and subsequent bacterial translocation?

A. PN enriched with glutamine.

B. PN enriched with branched-chain AAs.

C. Enteral nutrition (EN).

D. Zinc supplementation.

9. A female patient (weight 80 kg) in the intensive care unit has developed acute kidney injury caused by sepsis, and she requires intermittent hemodialysis on a daily basis to maintain her BUN/SCr ratio at 49:2.5 mg/dL. Currently, she is receiving appropriate antibiotics and is hemodynamically stable. She has also been receiving PN providing 72 g of AAs per day. What is the best recommendation for this patient's protein intake?

A. Reduce AAs to 40 g/day.

B. Reduce AAs to 64 g/day.

C. Increase AAs to 96 g/day.

D. Increase AAs to 160 g/day.

BPS Pharmacotherapy Specialty Examination Content.

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 1, Knowledge statements a-c, e, f, h, j-m, p, q
    b. Task 2, Knowledge statements a, b, d
    c. Task 3, Knowledge statements a-e
    d. Task 4, Knowledge statements a

I. FLUID MANAGEMENT

A. Distribution of total body fluid (TBF) (Figure 1)

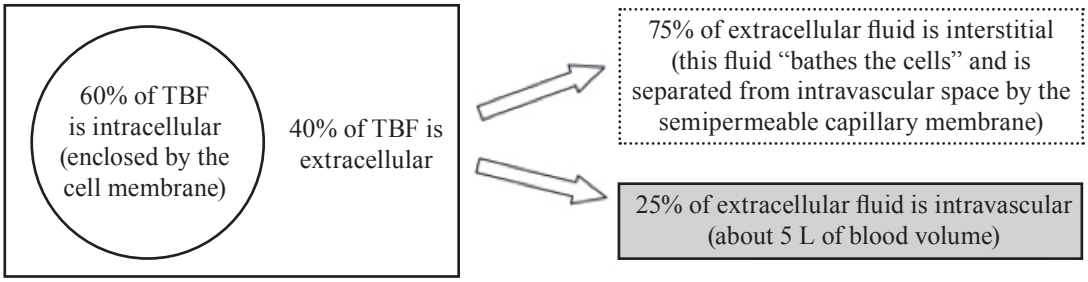
60% of TBF is intracellular (enclosed by the cell membrane)
40% of TBF is extracellular
75% of extracellular fluid is interstitial (this fluid "bathes the cells" and is separated from intravascular space by the semipermeable capillary membrane)
25% of extracellular fluid is intravascular (about 5 L of blood volume)

Figure 1. Distribution of total body fluid.
TBF = total body fluid.

1. Estimated as 60% of lean body weight (LBW) in men and 50% in women; a healthy adult (weight 70 kg) has about 42 L of fluid
2. Total body water is further divided into intracellular (IC) space and extracellular (EC) space.
   a. About 60% of TBF is IC, and 40% is EC; the IC and EC fluid compartments are separated by cell membranes, which are highly permeable to water.
   b. The EC compartment is also divided into the interstitial (IS) space and the intravascular space; the IS and intravascular fluid compartments are separated by the capillary membrane, which is permeable to almost all solutes except proteins.
      i. 75% of the EC fluid is in the IS space.
      ii. 25% of the EC fluid is in the intravascular space; the EC fluid in the intravascular space is known as *plasma*, and it measures about 3 L; if you also consider about 2 L of fluid found in red blood cells (thus, IC fluid), the total blood volume is about 5 L.
3. The approximate distribution of TBF into the IC and EC compartments with further distribution of the EC fluid into the IS and intravascular compartments is important to remember for determining the distribution of intravenous fluid.

B. Distribution of intravenous fluid (Table 1)

Table 1. Distribution of Intravenous Fluid

Intravenous Fluid	Infused Volume (mL)	Equivalent Intravascular Volume Expansion (mL)
Normal saline	1000	250
Lactated Ringer solution	1000	250
Normosol-R and Plasma-Lyte	1000	250
5% Dextrose	1000	100
Albumin 5%	500	500
Albumin 25%	100	500
Hydroxyethyl starch 6%	500	500

1. Crystalloids are intravenous fluids that can contain water, sodium (Na^+), chloride (Cl^-), and other electrolytes. Lactated Ringer solution is a crystalloid that contains mostly Na^+ and Cl^-, but also lactate, potassium (K^+), and calcium (Ca^{2+}). Normosol-R and Plasma-Lyte are crystalloids that contain mostly Na^+ and Cl^- but also acetate, K^+, and magnesium (Mg^{2+}). D_5W is also a crystalloid, but it should not be used for fluid resuscitation because of the smaller amount of fluid that remains in the intravascular compartment.
    a. Na and Cl^- do not freely cross into cells, but they will distribute evenly in the EC space.
    b. For 0.9% sodium chloride or lactated Ringer solution, only 25% remains in the intravascular space, and 75% distributes in the IS space; therefore, when 1 L of 0.9% sodium chloride or lactated Ringer solution is administered, about 250 mL of fluid remains in the intravascular compartment.
2. D_5W is isosmotic and, because of rapid metabolism, it has the net effect of administering "free" water.
    a. D_5W is metabolized to water and carbon dioxide.
    b. Water can cross any membrane in the body; therefore, it is evenly distributed in TBF ("free" because it is free to cross any membrane).
        i. Many experts avoid administering D_5W whenever possible in patients with neurologic injury and elevated intracranial pressure (ICP) because it can cross into cerebral cells, causing further elevation in ICP.
        ii. Some practitioners avoid the use of D_5W because of the risk of hyperglycemia, although D_5W contains only 5 g of dextrose/100 mL, which is equivalent to 17 kcal/100 mL.
    c. For D_5W, 60% distributes to the IC space and 40% distributes to the EC space. Of the 40% distributed to the EC space, 25% remains in the intravascular space, and 75% distributes to the IS space. Therefore, when 1 L of D_5W is administered intravenously, about 100 mL of fluid remains in the intravascular compartment.
3. Colloids include packed red blood cells, pooled human plasma (5% albumin, 25% albumin, and 5% plasma protein fraction), semisynthetic glucose polymers (dextran), and semisynthetic hydroxyethyl starch (hetastarch).
    a. Colloids are too large to cross the capillary membrane; therefore, they remain primarily in the intravascular space (although a small portion "leaks" into the IS space).
    b. Except for 25% albumin, administering 500 mL of colloid results in a 500-mL intravascular volume expansion.
    c. Because 25% albumin has an oncotic pressure about 5-fold that of normal plasma, it causes a fluid shift from the IS space into the intravascular space. For this reason, 100 mL of 25% albumin results in around 500 mL of intravascular volume expansion. This hyperoncotic solution should generally be avoided in patients requiring fluid resuscitation, because although the intravascular space expands, fluid shifts out of the IS space, potentially causing dehydration. It may be useful in patients who do not require fluid resuscitation but who could benefit from a redistribution of fluid (e.g., ascites, pleural effusions).
    d. Hydroxyethyl starch and dextran products have been associated with coagulopathy and kidney impairment. In addition to acute kidney injury, hydroxyethyl starch is associated with increased mortality in critically ill patients (JAMA 2013;309:678-88; N Engl J Med 2012;367:124-34).

C. Fluid Resuscitation
1. Intravascular fluid depletion can occur because of shock (hypovolemic or septic shock), and it is associated with reduced cardiac function and organ hypoperfusion.
2. Signs or symptoms (Box 1) usually occur when about 15% (750 mL) of blood volume is lost (e.g., hemorrhage) or shifts out of the intravascular space (e.g., severe sepsis).

Box 1. Signs and Symptoms of Intravascular Volume Depletion

Tachycardia (HR > 100 beats/minute)
Hypotension (SBP < 80 mm Hg)
Orthostatic changes in HR or BP
Increased BUN/SCr ratio > 20:1
Dry mucous membranes
Decreased skin turgor
Reduced urine output
Dizziness
Improvement in HR and BP after a 500- to 1000-mL fluid bolus

BP = blood pressure; BUN = blood urea nitrogen; HR = heart rate; SBP = systolic blood pressure; SCr = serum creatinine.

3. Fluid resuscitation is indicated for patients with signs or symptoms of intravascular volume depletion.
4. The goal of fluid resuscitation is to restore intravascular volume and to prevent organ hypoperfusion.
5. Because intravascular volume depletion can cause organ dysfunction and death, prompt resuscitation is necessary.
    a. Intravenous fluids are infused rapidly, preferably through a large-bore catheter.
    b. Intravenous fluids are administered as a 500- to 1000-mL bolus, (30 mg/kg in septic patients) after which the patient is reevaluated; this process is continued as long as signs and symptoms of intravascular volume depletion are improving (Box 1).

Table 2. Content of Common Crystalloid Solutions

	Contents (mEq/L)	**Osmolarity (mOsmol/L)**
Sodium chloride 0.9% (NS)	Na 154 Cl 154	308
Lactated Ringer (LR)	Na 130 Cl 109 K 4 Ca 3 Lactate 28	273
Normosol-R	Na 140 Cl 98 K 5 Mg 3 Acetate 27/Gluconate 23	295

Ca = calcium; Cl = chloride; K = potassium; Mg = magnesium; Na = sodium.

6. Crystalloids (0.9% sodium chloride or lactated Ringer solution) are recommended for fluid resuscitation in hypovolemia (Table 2).
    a. Lactated Ringer solution is historically preferred in surgery and trauma patients, but no evidence suggests superiority over normal saline for fluid resuscitation in these settings.
    b. The lactate in lactated Ringer solution is metabolized to bicarbonate, and it can theoretically be useful for metabolic acidosis; however, lactate metabolism is impaired during shock. Thus, lactated Ringer solution may be an ineffective source of bicarbonate.

c. Lactated Ringer solution has been considered to provide a more physiologic amount of Cl (109 mmol/L) than 0.9% sodium chloride (154 mmol/L). A balanced fluid regimen (e.g., lactated Ringer solution, Plasma-Lyte 148) was associated with a reduction in the incidence of acute kidney injury compared with a standard regimen (e.g., 0.9% sodium chloride, colloids containing Cl 120–130 mmol/L) (JAMA 2012;308:1566). In a multicenter, retrospective cohort study, a balanced solution (lactated Ringer) was compared with isotonic fluid (0.9% sodium chloride) in patients with sepsis. In these patients with vasopressor-dependent sepsis, those receiving balanced fluid had a lower risk of in-hospital mortality (Crit Care Med 2014;42:1585-91). More recent studies have shown that, when compared with 0.9% sodium chloride, balanced crystalloids result in a lower rate of a composite outcome of any cause of death, new renal replacement therapy, and persistent renal dysfunction in intensive care unit (ICU) patients. There was no difference found in hospital-free days in non-ICU patients (N Engl J Med 2018; 378:819-39).

7. There is no difference between crystalloids and colloids in the time to achieve fluid resuscitation or in patient outcomes. Colloids have not been shown to be superior to crystalloids, and they are associated with higher cost and some adverse effects. The following are examples of other, although controversial, uses of colloids:
   a. Colloids can be considered after fluid resuscitation with crystalloid (usually 4–6 L) has failed to achieve hemodynamic goals or after clinically significant edema limits the further administration of crystalloid.
   b. Albumin can be considered in patients with a low albumin concentration who have required a large volume of resuscitation fluids.
   c. Albumin (theoretically, 25% is preferred) can be considered in conjunction with diuretics for patients with clinically significant edema (e.g., pulmonary edema causing respiratory failure) and a low albumin concentration, when appropriately dosed diuretics are ineffective.

D. Maintenance intravenous fluids
   1. Maintenance intravenous fluids are indicated in patients who are unable to tolerate oral fluids.
   2. The goal of maintenance intravenous fluids is to prevent dehydration and to maintain a normal fluid and electrolyte balance.
   3. Maintenance intravenous fluids are typically administered as a continuous infusion through a peripheral or central intravenous catheter.
   4. Common methods of estimating the daily volume in children and adults:
      a. Administer 100 mL/kg for first 10 kg, followed by 50 mL/kg for the next 10–20 kg (i.e., 1500 mL for the first 20 kg) plus 20 mL/kg for every kilogram greater than 20 kg *or*
      b. Administer 20–40 mL/kg/day (for adults only).
      c. Adjust fluids according to the individual patient's input, output, and estimated insensible loss.
   5. A typical maintenance intravenous fluid is D_5W with 0.45% sodium chloride plus 20–40 mEq of potassium chloride per liter. The potassium chloride content can be adjusted for the individual patient.
   6. If 150 mEq of sodium bicarbonate is added to 850 mL of 0.9% sodium chloride, the resultant solution is equivalent to about 1.6% sodium chloride. When an infusion of 150 mEq of sodium bicarbonate per liter is indicated, it is recommended to add sodium bicarbonate to D_5W or sterile water for injection instead of 0.9% sodium chloride.

Patient Case

Questions 1 and 2 pertain to the following case.

A 65-year-old man (weight 80 kg) with a 3-day history of a body temperature of 102°F (38.9°C), lethargy, and productive cough is hospitalized for community-acquired pneumonia. His medical history includes uncontrolled hypertension and coronary artery disease. His vital signs include heart rate 104 beats/minute, blood pressure 112/68 mm Hg, and body temperature 101.4°F (38.6°C). His urine output is 10 mL/hour, K 4 mEq/L, BUN is 46 mg/dL, SCr is 1.7 mg/dL, and WBC is 10.4 × 103 cells/mm^3. Other laboratory values are normal.

1. Which is most appropriate at this time?
   A. Furosemide 40 mg intravenously.
   B. Albumin 25% 100 mL intravenously over 60 minutes.
   C. Lactated Ringer solution 1000 mL intravenously over 60 minutes.
   D. D_5W/0.45% sodium chloride plus potassium chloride 20 mEq/L to infuse at 110 mL/hour.

2. After 2 days of appropriate antibiotic treatment, the patient has a WBC of 9 × 103 cells/mm^3, and he is afebrile. His blood pressure is 135/85 mm Hg, and his urine output is 45 mL/hour. His albumin is 3.2 g/dL, BUN is 14 mg/dL, and SCr is 1.4 mg/dL. All other laboratory values are normal. His appetite is still poor, and he is not taking adequate fluids. He has peripheral intravenous access. Which option is most appropriate to initiate?
   A. Peripheral PN to infuse at 110 mL/hour.
   B. Albumin 5% 500 mL intravenously over 60 minutes.
   C. D_5W/0.45% sodium chloride plus potassium chloride 20 mEq/L to infuse at 110 mL/hour.
   D. Lactated Ringer solution to infuse at 110 mL/hour.

II. OSMOLALITY

A. Plasma osmolality is normally 275–290 mOsm/kg.
   1. Terminology
      a. Osmolality is a measure of the osmoles of solute per kilogram of solvent (Osm/kg), whereas osmolarity is a measure of osmoles of solute per liter of solution (Osm/L).
      b. Plasma osmolarity (mOsm/L) can be calculated as osmolality × 0.995, showing that there is no clinically significant difference between them (i.e., plasma osmolarity is about 1% lower than plasma osmolality).
   2. Plasma osmolality is maintained within a normal range by thirst and secretion of arginine vasopressin (i.e., antidiuretic hormone [ADH]) from the posterior pituitary.
   3. Sodium salts are the primary determinant of plasma osmolality, and they regulate fluid shifts between the IC and EC fluid compartments.
   4. Plasma osmolality (in milliosmoles per kilogram) can be estimated: (2 × Na^+ mEq/L) + (glucose mg/dL/18) + [(BUN mg/dL) ÷ 2.8].
   5. Increases in plasma osmolality cause an osmotic shift of fluid into the plasma, resulting in cellular dehydration and shrinkage.
   6. Decreases in plasma osmolality cause an osmotic shift of fluid into cells, resulting in cellular overhydration and swelling.

B. Intravenous fluids can be classified by their osmolarity relative to plasma.
   1. Isotonic fluid does not result in a fluid shift between fluid compartments because the osmolarity is similar to plasma.
   2. Hypertonic fluid, such as NaCl 3%, can cause fluid to shift from the IC to the EC compartment, with subsequent cellular dehydration and shrinkage.
   3. Hypotonic fluid, such as NaCl 0.225%, with an osmolarity less than 150 mOsm/L can cause fluid to shift from the EC to the IC compartment, with subsequent cellular overhydration and swelling.
      a. Red blood cell swelling can cause cell rupture (i.e., hemolysis).
      b. Brain cells can swell, causing cerebral edema and herniation; this is most likely to occur with acute hyponatremia (occurring in less than 2 days).

C. Definitions
   1. Equivalent weight = Molecular weight (MW) divided by valence.
      a. A milliequivalent (mEq) = 1/1000 of an equivalent.
      b. Examples of equivalent weight are shown in Table 3.
      c. 1 mol = equivalent weight

Table 3. Electrolyte MW, Valence, and Equivalent Weight

Electrolyte	MW	Valence	Equivalent Weight (g)
Sodium	23	1	23
Potassium	39	1	39
Chloride	35.5	1	35.5
Magnesium	24	2	12

MW = molecular weight.

   2. Osmoles = number of particles in a solution (assuming complete dissociation).
      a. A milliosmole = 1/1000 of an osmole.
      b. Examples of osmoles are shown in Table 4.

Table 4. Osmoles

Salt	Osmoles
NaCl	2
KCl	2
$CaCl_2$	3

$CaCl_2$ = calcium chloride; KCl = potassium chloride; NaCl = sodium chloride.

   3. Converting MW to milliequivalents (Box 2)

Box 2. Converting MW to Milliequivalents

Convert 23.4% NaCl (concentrated NaCl) to mEq/mL
MW of NaCl = 23 + 35.5 = 58.5 (add MW of Na + Cl)
$\frac{23.4\text{ g}}{100\text{ mL}} \times \frac{1\text{ equiv}}{58.5\text{ g}} \times \frac{1000\text{ mEq}}{1\text{ equiv}} = 4\text{ mEq/mL}$

MW = molecular weight; NaCl = sodium chloride.

D. Calculating the osmolarity of intravenous fluids in milliosmoles per liter
   1. The osmotic coefficient can be used to calculate the osmolarity of intravenous fluids because salt forms do not completely dissociate in solution. However, commercially available products often have different reported osmolarities than if if the osmolarity is calculated using the osmotic coefficient.
      a. With sodium chloride, for example, there is some ionic attraction between Na^+ and Cl, and they do not completely dissociate; rather, they are about 93% dissociated in solution (thus, the osmotic coefficient is 0.93).
      b. In clinical practice and in commercially available products, most do not consider the osmotic coefficient when calculating the osmolarity of sodium chloride or other electrolytes. In reality, the osmotic coefficient is probably not clinically relevant (but it is used in the following examples for completeness).
   2. Normal saline (0.9% sodium chloride) (Table 5)

Table 5. Calculation for Normal Saline Using the Osmotic Coefficient

Molecular Weight	Osmoles	Osmotic Coefficient
58.5 g/mol	2	0.93
$\frac{0.9\text{ g}}{100\text{ mL}} \times \frac{1\text{ mol}}{58.5\text{ g}} \times \frac{2\text{ Osm}}{1\text{ mol}} \times \frac{1000\text{ mOsm}}{1\text{ Osm}} \times \frac{1000\text{ mL}}{1\text{ L}} \times 0.93 = 287\text{ mOsm/L}$		

   3. D_5W (MW 198 g/mol) (Box 3)

Box 3. Calculation for D_5W

$$\frac{5\text{ g} \times}{100\text{ mL}} \times \frac{1\text{ mol}}{198\text{ g}} \times \frac{1000\text{ mOsm}}{1\text{ mol}} \times \frac{1000\text{ mL}}{1\text{ L}} = 252.5\text{ mOsm/L}$$

   4. Osmolarity of D_5W/normal saline using the osmotic coefficient = 252.5 mOsm/L + 287 mOsm/L = 539.5 mOsm/L.
   5. Osmolarity of normal saline + potassium chloride 20 mEq/L (Box 4)

Box 4. Calculation for NS plus KCl Using the Osmotic Coefficient

Step 1: Convert mEq to weight (g)

$$20\text{ mEq} \times \frac{1\text{ equiv}}{1000\text{ mEq}} \times \frac{74.5\text{ g}}{1\text{ equiv}} = 1.49\text{ g of KCl}$$

Step 2: Calculate mOsm/L

$$\frac{1.49\text{ g}}{\text{L}} \times \frac{1\text{ mol}}{74.5\text{ g}} \times \frac{2\text{ Osm}}{1\text{ mol}} \times \frac{1000\text{ mOsm}}{1\text{ Osm}} = 40\text{ mOsm/L}$$

Step 3: Add osmolarity of NS + KCl = 287 mOsm/L + 40 mOsm/L = 327 mOsm/L

NS = normal saline; KCl = potassium chloride.

III. HYPERTONIC SALINE

A. Concentration: Typically use 3% (954 mOsm/L), 7.5% (2393 mOsm/L), or 23.4% (7462 mOsm/L). Sodium chloride 3% and 23.4% are available commercially, whereas other concentrations must be extemporaneously prepared.

B. Common uses of hypertonic saline
   1. Hypertonic saline is used in traumatic brain injury to reduce an elevated ICP and thereby increase cerebral perfusion pressure. It is typically used if sustained ICP is greater than 20 mm Hg as measured with an ICP monitor.
   2. Hypertonic saline is used for symptomatic hyponatremia (symptoms described later in the Hyponatremia section).
      a. Symptoms generally do not occur unless serum sodium is 120 mEq/L or less, and they increase in severity as Na^+ decreases.
      b. Symptoms of severe hyponatremia include coma and seizures.
      c. In an effort to prevent severe symptoms from occurring, some practitioners treat asymptomatic or moderately symptomatic (e.g., lethargy, confusion) hyponatremia before serum sodium concentrations reach 120 mEq/L or less because of the increased risk of severe symptoms below this concentration.

C. Inappropriate use of hypertonic saline
   1. Chronic asymptomatic hyponatremia
      a. Asymptomatic syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is usually treated with fluid restriction of less than 800 mL of fluid per day.
      b. Hyponatremia is generally a water problem (i.e., an excess of free water) rather than a deficiency of Na; thus, hypertonic saline makes little sense in the absence of symptoms (see Hyponatremia section).
   2. Hyponatremia associated with severe hyperglycemia (pseudohyponatremia; i.e., diabetic ketoacidosis)
      a. Typically, serum sodium decreases in a nonlinear fashion in response to hyperglycemia (i.e., Na^+ decreases by about 1.6 mEq/L for every 100-mg/dL elevation in glucose of 100–400 mg/dL; however, another version of the formula shows that Na^+ decreases by about 2.4 mEq/L for every 100-mg/dL elevation in glucose above 100 mg/dL). Corrected Na^+ = serum Na^+ + [1.6 (glucose – 100)/100]
      b. As hyperglycemia is corrected with insulin, the serum sodium will normalize.
   3. Hyponatremia associated with hypervolemia (i.e., heart failure leads to tissue hypoperfusion, which triggers ADH secretion, causing reabsorption of water from the kidneys and leading to hyponatremia)
      a. In general, this situation is treated with fluid restriction or diuresis.
      b. Symptomatic hyponatremia is uncommon in patients with heart failure.
      c. Hypertonic saline could be considered in symptomatic patients; however, they may also need diuresis to prevent worsening volume overload.

D. Preparation of hypertonic saline (Commercially available products should be used whenever possible to minimize the risk of error) (Figure 2)

Steps	Example
Choose base solutions	For this example, use concentrated NaCl available as 23.4% vials and sterile water to make 1000 mL of 7.5% HS
Set up alligation	23.4% → 7.5% ← 0
Add and subtract	23.4% → 7.5% ← 0 7.5 parts (from 23.4% NaCl) 15.9 parts (from sterile water) 23.4 parts total
Divide	7.5 parts/23.4 parts = *x*/1000 mL; *x* = 320.5 mL of 23.4% NaCl 15.9 parts/23.4 parts = *x*/1000 mL; *x* = 679.5 mL of sterile water

Figure 2. Calculations to prepare hypertonic saline.
HS = hypertonic saline; NaCl = sodium chloride.

E. Hypertonic saline dose
   1. Dose options for traumatic brain injury and other neurological injuries
      a. 3% hypertonic saline 250 mL or 2–4 mL/kg intravenously over 1–15 minutes administered for elevated ICP
      b. 23.4% hypertonic saline 30 mL over 20–30 minutes administered for elevated ICP
         i. Standing orders such as 30 mL every 4–6 hours are sometimes used or as needed for a sustained ICP greater than 20 mm Hg.
         ii. If hypertonic saline is needed for prolonged reduction in ICP, a 3% hypertonic saline continuous infusion may be recommended.
   2. Dose options for patients with symptomatic hyponatremia
      a. Treatment of patients with symptomatic hyponatremia involves a small but quick increase in serum sodium by 0.75–1 mEq/L/hour to a concentration of 120 mEq/L, though not more than 10–12 mEq in 24 hours. Next, the infusion can be reduced so that Na^+ increases by 0.5 mEq/L/hour. For severe symptoms, it is reasonable to increase serum sodium by up to 2 mEq/L/hour for a short time, as long as the maximum change of 10–12 mEq in 24 hours is not exceeded. If hypertonic saline is used for mild symptoms, a slower change in serum sodium of 0.5 mEq/L/hour would be appropriate, although some would avoid hypertonic saline altogether. Some protocols are more conservative, recommending a maximum change of 8 mEq in 24 hours.
      b. Estimate an infusion rate of 3% hypertonic saline by multiplying ideal body weight (IBW) by desired rate of serum sodium increase per hour. (Note: IBW is used to avoid overdosing patients with obesity.)
         i. For example, 70 kg × 1 mEq/L/hour = 70 mL/hour to increase serum sodium by 1 mEq/L in 1 hour. The infusion can be adjusted to achieve goal changes in serum sodium.
         ii. Infusion rate of 3% hypertonic saline is generally 1–2 mL/kg/hour.
         iii. In general, 3% hypertonic saline is not recommended in asymptomatic patients; if used in an asymptomatic patient, the administration rate should generally not exceed 0.5–1 mL/kg/hour.
      c. Alternatively, some practitioners recommend a 250-mL bolus of 2%–3% hypertonic saline over 30 minutes or 50 mL of 3% hypertonic saline administered as a bolus every 30 minutes for two doses.

F. Administration of hypertonic saline
   1. Use central intravenous access because the osmolarity is greater than 900 mOsm/L.
   2. If no central line is available, consider using 2% hypertonic saline.
   3. Some practitioners use 3% hypertonic saline through a peripheral intravenous access site in an emergency, because the osmolarity is close to the cutoff range for peripheral administration. Recent literature suggests that 3% sodium chloride can safely be administered through a peripheral line (J Neurosci Nurs 2017;49:191-5). If a peripheral site is used, use a large vein and monitor for phlebitis.

G. Clinical goals and monitoring for administering hypertonic saline in patients with symptomatic hyponatremia
   1. Goals
      a. Decrease symptoms (described later).
      b. Safe serum sodium achieved usually in the range of 120–125 mEq/L to avoid adverse neurologic outcomes. Note that the immediate goal for patients with symptomatic hyponatremia is not necessarily a normal serum sodium.
      c. Reached maximum safe amount of change in serum sodium
         i. Maximum safe amount of change is generally regarded as 10–12 mEq/L in 24 hours.
         ii. Some practitioners suggest a maximum change of 8 mEq/L in 24 hours.
   2. Monitoring of serum sodium every 1–4 hours depending on severity of symptoms

H. Complications of hypertonic saline
   1. Osmotic demyelination syndrome (includes central pontine and extrapontine myelinolysis) can occur with rapid correction of hyponatremia.
      a. It is characterized initially by lethargy and affect changes, followed by permanent neurologic damage, including paraparesis, quadriparesis, dysarthria, dysphagia, and coma.
      b. It is more likely to occur with rapid correction of chronic hyponatremia than with acute hyponatremia. This partly explains why it is advisable not to administer hypertonic saline in patients with chronic asymptomatic hyponatremia.
      c. Prevent this complication by avoiding changes in serum sodium of more than 10–12 mEq/L in 24 hours or more than 18 mEq/L in 48 hours.
   2. Hypokalemia can occur with large volumes of hypertonic saline.
   3. Hyperchloremic acidosis can result from the administration of chloride salts (i.e., sodium chloride). It can be prevented by administering hypertonic saline in a 1:1 or 2:1 ratio of sodium chloride and sodium acetate or using fluid with less chloride content.
   4. Hypernatremia
   5. Phlebitis if administered in a peripheral vein
   6. Heart failure
      a. Fluid overload can result from initial volume expansion.
      b. Over time, hypertonic saline can have a diuretic effect, leading to intravascular volume depletion.
   7. Coagulopathy caused by platelet dysfunction
   8. Hypotension if hypertonic saline is administered rapidly

I. Other considerations when using hypertonic saline. Because hypokalemia can cause hyponatremia, remember to correct K^+ depletion if present. As K^+ is replaced, serum sodium will increase.

IV. HYPOTONIC INTRAVENOUS FLUIDS

A. Hypotonic fluids administered intravenously can cause cell hemolysis and patient death.
   1. Albumin 25% diluted with sterile water to make albumin 5% has an osmolarity of about 60 mOsm/L, which can cause hemolysis.
   2. "Quarter normal saline," or 0.225% sodium chloride, has an osmolarity of 77 mOsm/L and can cause hemolysis.

B. Avoid using intravenous fluid with an osmolarity less than 150 mOsm/L.
   1. Sterile water alone should *never* be administered intravenously.
   2. Some prescribers use hypotonic saline for a patient with hypernatremia.
      a. In reality, a patient with mild hypernatremia generally needs water, not additional Na^+.
      b. Therefore, for patients with hypernatremia, enteral administration of water is preferable.
      c. If the enteral route is unavailable, recommend D_5W administered intravenously.

C. Prevent a potentially fatal error by recommending one of the following alternatives to 0.225% sodium chloride:
   1. Recommend changing 0.225% sodium chloride to D_5W alone or a combination of D_5W and 0.225% sodium chloride.
   2. Alternatively, if there are concerns related to hyperglycemia with using D_5W (50 g of dextrose or 170 kcal/L), recommend using 2.5% dextrose and 0.225% sodium chloride.
   3. Alternatively, potassium chloride can be added to increase osmolarity.
   4. Recommend administering water enterally (by mouth or feeding tube).
   5. If 0.225% sodium chloride is used, recommend use by central venous line.

V. HYPONATREMIA AND HYPO-OSMOLAL STATES

A. Sodium salts are the primary determinants of plasma osmolality (and subsequent fluid shifts between the IC and EC compartments).
   1. A reduction in serum sodium to less than 136 mEq/L usually correlates with a reduction in plasma osmolality.
   2. Hyponatremia with subsequent hypo-osmolality causes fluid to shift into cells (cellular overhydration). Hypotonic hyponatremia can be divided into three types according to volume status (Table 6).

Table 6. Classification of Hyponatremia

	Hypovolemic Hyponatremia	Euvolemic Hyponatremia	Hypervolemic Hyponatremia
Description	Deficit of both Na^+ and fluid, but total Na^+ is decreased more than total body water	Normal total body Na^+ with excess fluid volume (i.e., dilutional)	Excess Na^+ and fluid, but fluid excess predominates
Example	Fluid loss (e.g., emesis, diarrhea, fever), third spacing, renal loss (diuretics), cerebral salt wasting	SIADH, medications	Heart failure, cirrhosis, nephrotic syndrome
Diagnosis	Urine $Na^+ < 25$ mEq/L indicates nonrenal loss of Na^+ (e.g., emesis, diarrhea); urine $Na^+ > 40$ mEq/L indicates renal loss of Na^+	Urine osmolality > 100 mOsm/kg (indicates impaired water excretion in presence of plasma osmolality < 275 mOsm/kg); urine sodium > 40 mEq/L	Urine $Na^+ < 25$ mEq/L indicates edematous disorders (i.e., heart failure, cirrhosis, nephrotic syndrome); urine $Na^+ > 25$ mEq/L indicates acute or chronic renal failure
Treatment	Fluid resuscitation (see above); in patients with cerebral salt wasting because of a neurologic injury, hyponatremia can be prevented in patients with neurologic injuries with sodium chloride tablets or fludrocortisone	If drug-induced SIADH, remove offending agent; fluid restriction; demeclocycline; vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), some institutions use urea	Sodium and water restriction; treat underlying cause; vasopressin receptor antagonists (e.g., conivaptan, tolvaptan), diuretics

Na^+ = sodium; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

3. In select cases, hyponatremia is associated with either a normal or an elevated plasma osmolality.
    a. This is known as *pseudohyponatremia*, because Na^+ content in the body is not actually reduced. Instead, Na^+ shifts from the EC compartment into the cells in an attempt to maintain plasma osmolality in a normal range. Another adaptation to increased plasma osmolality is the shift of water from inside cells to the EC compartment, which further dilutes the Na^+ concentration.
        i. Severe hyperlipidemia can be associated with a normal or elevated plasma osmolality.
        ii. Severe hyperglycemia (i.e., during diabetic ketoacidosis) is associated with an elevated plasma osmolality.
    b. Once the underlying condition is corrected, Na^+ will shift out of the cells, and hyponatremia will resolve.

B. Causes of hyponatremia
1. Replacement of lost solute with water
    a. Loss of solute (e.g., vomiting, diarrhea) usually involves the loss of isotonic fluid; therefore, alone, it will not cause hyponatremia.
    b. After the loss of isotonic fluid, hyponatremia can develop when the lost fluid is replaced with water.
    c. A common cause of hyponatremia in hospitals is the postoperative administration of hypotonic fluid.
2. Volume depletion and organ hypoperfusion stimulate ADH secretion to increase water reabsorption in the collecting tubules, potentially causing hyponatremia.
3. SIADH and cortisol deficiency are both related to the excessive release of ADH.

4. Medications, including thiazide diuretics, antiepileptic drugs (e.g., carbamazepine, oxcarbazepine), and antidepressants (especially selective serotonin reuptake inhibitors but also tricyclic antidepressants), can cause hyponatremia. Drug-induced hyponatremia is more likely to occur in older adults and in those who drink large volumes of water.
5. Renal failure impairs the ability to excrete dilute urine, predisposing to hyponatremia.

C. Symptoms of hyponatremia (Table 7)

Table 7. Symptoms of Hyponatremia

Serum Sodium (mEq/L)	Clinical Manifestations
120–125	Nausea, malaise
115–120	Headache, lethargy, obtundation, unsteadiness, confusion
< 115	Delirium, seizure, coma, respiratory arrest, death

1. Symptoms are generally attributable to hypo-osmolality, with subsequent water movement into brain cells causing cerebral edema.
2. If hyponatremia occurs chronically, cerebral cell swelling is prevented by osmotic adaptation.
   a. Solutes move out of brain cells to prevent the osmotic shift of water into brain cells.
   b. For this reason, patients with chronic hyponatremia may show less severe or no symptoms.
3. Neurologic symptoms are related to the rate of change in the serum sodium and to the degree of change in serum sodium.
4. Acute hyponatremia occurs over 1–3 days.

D. Treatment of hyponatremia
   1. Treat underlying cause.
   2. Raise serum sodium at a safe rate, defined as a change no greater than 10–12 mEq/L in 24 hours.
   3. Treatment depends on volume status, the presence and severity of symptoms, and the onset of hyponatremia.
      a. If the patient is euvolemic or edematous, there are typically two treatment options:
         i. Fluid restriction (to less than 800 mL/day) is the typical first-line recommendation for asymptomatic patients. Note that sodium administration is not recommended for asymptomatic patients because it can worsen edema.
         ii. Vasopressin antagonists (e.g., intravenous conivaptan, oral tolvaptan) can be used in euvolemic (i.e., SIADH) or hypervolemic (i.e., heart failure) patients to promote aquaresis, increase serum sodium, alleviate symptoms, and reduce weight; however, this approach is costly and has not been shown to improve clinical outcomes (i.e., fall prevention, hospitalization, hospital length of stay, quality of life, mortality) in prospective randomized controlled trials. Vasopressin antagonists are substrates and inhibitors of cytochrome P450 3A4 isoenzymes. Monitor for drug interactions with other 3A4 inhibitors that could increase effect and lead to a rapid increase in serum sodium. Fluid restriction in combination with a vasopressin antagonist during the first 24 hours can also increase the risk of overly rapid correction of serum sodium. If needed, fluid restriction can be used after 24 hours. Tolvaptan should not be administered for more than 30 days to minimize risk of liver injury. Monitor for recurrence of hyponatremia once treatment is discontinued. In hypervolemic hyponatremia, diuretics can also be used.

b. If the patient has intravascular volume depletion, volume must be replaced first with intravenous crystalloids (e.g., 0.9% sodium chloride).
   i. Until intravascular volume is restored, the patient will continue to secrete ADH, causing water reabsorption and subsequent hyponatremia.
   ii. Once intravascular volume is restored, ADH secretion will decrease, causing water to be excreted. This can lead to a rapid correction of serum sodium; careful monitoring is necessary to prevent overly rapid correction.
   iii. Volume status can be assessed by skin turgor, jugular venous pressure, and urine sodium.

c. Once intravascular volume is restored, patients who experienced volume depletion, diuretic-induced hyponatremia, or adrenal insufficiency may still need Na^+.
   i. The amount of Na^+ (in milliequivalents) needed to raise the serum sodium to a safe concentration of about 120 mEq/L is estimated using LBW as follows: 0.5 (LBW) × (120 − Na^+) for women (multiply LBW by 0.6 for men). LBW has been estimated using weight in kilograms and height in centimeters for men as LBW = [(0.3)(kg) + (0.3)(cm) − 29] or for women as LBW= [(0.3)(kg) + (0.4)(cm) − 43]; formula published in 1966 (J Clin Pathol 1966;19:389).
   ii. Alternatively, this equation can be modified to estimate the Na^+ deficit in the following manner: 0.5 (LBW) × (140 − Na^+) for women (multiply LBW by 0.6 for men). If calculating the Na^+ deficit, it is recommended to administer 25%–50% of the deficit during the first 24 hours to prevent the overly rapid correction of serum sodium.
   iii. Regardless of the method used to estimate Na^+ replacement, the amount of Na^+ administered should be guided by serial serum sodium concentrations (e.g., every 4 hours).

d. Patients with symptomatic hyponatremia should be treated with hypertonic saline (see Hypertonic Saline section).

4. Correct hypokalemia, if present, with hyponatremia.
   a. Hypokalemia will cause a reduction in serum sodium because Na^+ enters cells to account for the reduction in IC K^+ to maintain cellular electroneutrality.
   b. Administration of K^+ will help correct hyponatremia.
   c. Use caution when giving K^+ to prevent overly rapid correction of serum sodium.

Patient Case

Questions 3–5 pertain to the following case.

A 72-year-old woman (weight 60 kg) with a history of hypertension has developed hyponatremia after starting hydrochlorothiazide 3 weeks earlier. She experiences dizziness, fatigue, and nausea. Her serum sodium is 116 mEq/L. Her blood pressure is 86/50 mm Hg, and heart rate is 122 beats/minute.

3. In addition to discontinuing hydrochlorothiazide, which initial treatment regimen is best?
   A. Administer 0.9% sodium chloride infused at 100 mL/hour.
   B. Administer 0.9% sodium chloride 500-mL bolus.
   C. Administer 3% sodium chloride infused at 60 mL/hour.
   D. Administer 23.4% sodium chloride 30-mL bolus as needed.

Patient Case *(Cont'd)*

4. Which is the best treatment goal for the first 24 hours in correcting the patient's serum sodium from her initial value of 116 mEq/L?
   A. Increase Na+ concentration to 140 mEq/L.
   B. Increase Na+ concentration to 132 mEq/L.
   C. Increase Na+ concentration to 126 mEq/L.
   D. Maintain serum sodium of 116–120 mEq/L.

5. One day later, the patient has improved somewhat. Her blood pressure is 122/80 mm Hg, and heart rate is 80 beats/minute. Her serum sodium is 120 mEq/L, and K+ is 3.2 mEq/L; she still feels tired. She is eating a regular diet. Her ECG is normal. Which is the best recommendation?
   A. D_5W/0.9% sodium chloride plus potassium chloride 40 mEq/L to infuse at 100 mL/hour.
   B. 0.9% sodium chloride infused at 100 mL/hour.
   C. 3% sodium chloride infused at 60 mL/hour.
   D. Potassium chloride 20 mEq by mouth every 6 hours for 4 doses.

VI. HYPERNATREMIA AND HYPEROSMOLAL STATES

A. Hyperosmolality with serum sodium greater than 145 mEq/L
   1. The osmotic gradient associated with hypernatremia causes water movement out of cells and into the EC space.
   2. Symptoms are related primarily to the dehydration of brain cells.

B. Causes of hypernatremia
   1. Loss of water because of fever, burns, infection, renal loss (e.g., diabetes insipidus), gastrointestinal (GI) loss
   2. Retention of Na^+ because of the administration of hypertonic saline or any form of Na^+
   3. Certain neurologic injuries receive hypertonic saline to target a higher sodium goal

C. Prevention of hypernatremia through osmoregulation
   1. Plasma osmolality is maintained at 275–290 mOsm/kg, despite changes in water and Na^+ intake.
   2. Hypernatremia is prevented first by the release of ADH, causing water reabsorption.
   3. Hypernatremia is also prevented by thirst.
      a. Hypernatremia occurs primarily in adults with altered mental status who have an impaired thirst response or do not have access to or the ability to ask for water.
      b. Hypernatremia can also occur in infants.

D. Cerebral osmotic adaptation
   1. Similar to patients with hyponatremia, patients with chronic hypernatremia can have cerebral osmotic adaptation.
      a. Brain cells take up solutes, Na^+, and K^+, thus limiting the osmotic gradient between the IC and EC fluid compartments.
      b. This prevents cellular dehydration, and it will increase the brain volume toward a normal value, despite hypernatremia.
   2. Because of osmotic adaptation, patients with chronic hypernatremia may be asymptomatic.

E. Symptoms of hypernatremia are primarily neurologic.
   1. Similar to hyponatremia, the symptoms of hypernatremia are related to the rate of increase in plasma osmolality and the degree of increase in plasma osmolality.
   2. Earlier symptoms include lethargy, weakness, and irritability.
   3. Symptoms can progress to twitching, seizures, coma, and death if serum sodium is greater than 158 mEq/L. However, some neurologic injuries may have higher serum sodium targets.
   4. Cerebral dehydration can cause cerebral vein rupture with subsequent intracerebral or subarachnoid hemorrhage.

F. Treatment of hypernatremia
   1. Rapid correction of chronic hypernatremia can result in cerebral edema, seizure, permanent neurologic damage, and death.
      a. With osmotic adaptation, the brain volume is raised toward normal despite an elevated serum osmolarity.
      b. Osmotic adaptation combined with a rapid reduction in plasma osmolality can cause an osmotic gradient, causing water to move into brain cells with subsequent cerebral edema.
   2. In patients with symptomatic hypernatremia, serum sodium should be reduced slowly by no more than 0.5 mEq/L/hour or 12 mEq/L/day.
   3. Treat hypernatremia by replacing water deficit slowly over several days to prevent overly rapid correction of serum sodium.
      a. Using LBW, the estimated water deficit (in liters) is (0.4 × LBW) × [(Serum sodium/140) − 1] in women (multiply LBW by 0.5 in men).
      b. Note that in women and men, total body water is typically about 50% and 60%, respectively, of LBW. Thus, some sources recommend a variation on the earlier equation as follows: Water deficit = (0.5 × LBW) × [(Serum sodium/140) − 1] in women (multiply LBW by 0.6 in men). However, patients with hypernatremia are generally water depleted; thus, the equation using the lower values above (i.e., 40% or 0.4 and 50% or 0.5) is reasonable.
   4. Administer free water orally or intravenously as D_5W.
   5. If concurrent Na^+ and water depletion occur (e.g., vomiting, diarrhea, diuretic-induced depletion), use a combination of D_5W and 0.225% sodium chloride.
   6. If the patient is hypotensive because of volume depletion, first restore intravascular volume with 0.9% sodium chloride to restore tissue perfusion. Normal saline is the preferred crystalloid for fluid resuscitation, and it is still relatively hypotonic in the patient with hypernatremia.
   7. Patients with severe central diabetes insipidus may require desmopressin (DDAVP) (a synthetic analog of ADH) to replace insufficient or absent endogenous ADH. Diabetes insipidus is marked by increased urine output and decreased urine specific gravity.

Patient Case

6. A 74-year-old woman (weight 50 kg) has been receiving isotonic tube feedings at 60 mL/hour for the past 8 days through her gastrostomy feeding tube. She recently had an ischemic stroke; she is responsive but does not communicate. Her serum sodium was 142 mg/dL on the day the isotonic formula was initiated, and it has risen steadily to 149, 156, and 159 mg/dL on days 3, 4, and 8, respectively, after the start of the tube feedings. What is the best treatment for her hypernatremia?

   A. Administer sterile water intravenously at 80 mL/hour.

   B. Administer D_5W intravenously at 80 mL/hour.

   C. Administer D_5W/0.225% sodium chloride intravenously at 80 mL/hour.

   D. Administer water by enteral feeding tube 200 mL every 6 hours.

VII. DISORDERS OF K^+

A. Normal plasma potassium concentrations are 3.5–5 mEq/L.

B. K^+ is the primary IC cation (maintains electroneutrality with Na, the primary EC cation).

C. K^+ balance is maintained between the IC and EC compartments by several factors, including the following:
   1. β_2-Adrenergic stimulation (caused by epinephrine) promotes cellular uptake of K^+.
   2. Insulin promotes cellular uptake of K^+.
   3. Plasma potassium concentration directly correlates with movement of K^+ in and out of cells because of passive shifts based on the concentration gradient across the cell membrane. (A normal response to diarrhea-induced hypokalemia is for K^+ to shift out of the cells passively, minimizing the reduction in plasma potassium concentration.)

D. Normal plasma concentrations of K^+ are maintained by renal excretion.

E. Hypokalemia (K^+ concentration less than 3.5 mEq/L)
   1. Causes of hypokalemia
      a. Reduced intake seldom causes hypokalemia, because renal excretion is minimized because of increased renal tubular absorption.
      b. Increased shift of K^+ into cells can occur with the following:
         i. Alkalosis
         ii. Insulin or a carbohydrate load
         iii. β_2-Receptor stimulation caused by stress-induced epinephrine release or administration of a β-agonist (e.g., albuterol, dobutamine)
         iv. Hypothermia
      c. Increased GI losses of K^+ can occur with vomiting, diarrhea, intestinal fistula or enteral tube drainage, and chronic laxative abuse.
      d. Increased urinary losses can occur with mineralocorticoid excess (e.g., aldosterone) and diuretic use (e.g., loop and thiazides).
      e. Hypomagnesemia is commonly associated with hypokalemia caused by increased renal loss of K^+; correction of plasma potassium requires simultaneous correction of serum magnesium.
   2. Symptoms of hypokalemia generally occur when plasma potassium is less than 3 mEq/L and can include the following:
      a. Muscle weakness occurs most commonly in the lower extremities, but it can progress to the trunk, upper extremities, and respiratory muscles. Muscle weakness in the GI tract can manifest as paralytic ileus, abdominal distention, nausea, vomiting, and constipation.
      b. ECG changes (flattened T waves or elevated U wave) occur.
      c. Cardiac arrhythmias (bradycardia, heart block, ventricular tachycardia, ventricular fibrillation) occur.
      d. Digoxin toxicity can occur despite normal serum digoxin concentrations in the presence of hypokalemia.
      e. Rhabdomyolysis can occur because hypokalemia can cause reduced blood flow to skeletal muscle.
   3. Treatment of hypokalemia
      a. K^+ deficit can be estimated as 200–400 mEq of K^+ for every 1 mEq/L reduction in plasma potassium (assuming a normal distribution of K^+ between EC and IC compartments).
      b. Although the K^+ deficit can be estimated, K^+ replacement is guided by K^+ concentrations; recheck every 2–4 hours if K^+ is less than 3 mEq/L.

c. Potassium chloride is the preferred salt in patients with concurrent metabolic alkalosis, because these patients typically lose Cl^- through diuretics or GI loss. This is the most common presentation of hypokalemia.
d. Potassium acetate can be administered intravenously, or potassium bicarbonate can be administered orally for patients with a metabolic acidosis that requires frequent K^+ supplementation.
e. Guidelines for administering K^+ (Table 8)

Table 8. K^+ Replacement

Plasma K^+ (mEq/L)	Treatment[a]	Comments
3–3.5	Oral KCl 40–80 mEq/day if no signs or symptoms (doses > 60 mEq should be divided to avoid GI adverse effects)	Recheck K^+ daily
2.5–3	Oral KCl 120 mEq/day (in divided doses) or IV 60–80 mEq administered at 10–20 mEq/hr if signs or symptoms	Monitor K^+ closely (i.e., 2 hr after infusion)
2–2.5	IV KCl 10–20 mEq/hr	Consider continuous ECG monitoring
< 2	IV KCl 20–40 mEq/hr	Requires continuous ECG monitoring

[a]Treatment doses are for patients with normal kidney function and should be reduced for patients with kidney dysfunction or older adults.
ECG = electrocardiogram; GI = gastrointestinal; IV = intravenous; KCl = potassium chloride; K^+ = potassium.

i. Patients without ECG changes or symptoms of hypokalemia can be treated with oral supplementation.
ii. Avoid mixing K^+ in dextrose, which can cause insulin release with a subsequent IC shift of K^+.
iii. To avoid irritation, no more than about 60–80 mEq/L should be administered through a peripheral vein.
iv. Recommended infusion rate is 10–20 mEq/hour to a maximum of 40 mEq/hour.
v. Patients who receive K^+ at rates faster than 10–20 mEq/hour should be monitored using a continuous ECG.

F. Hyperkalemia
1. Causes of hyperkalemia
a. Increased intake
b. Shift of K^+ from the IC to the EC compartment causes hyperkalemia and can occur with the following:
i. Acidosis
ii. Insulin deficiency
iii. β-Adrenergic blockade
iv. Digoxin overdose
v. Rewarming after hypothermia (e.g., after cardiac surgery)
vi. Succinylcholine
c. Reduced urinary excretion can occur with:
i. Kidney dysfunction
ii. Intravascular volume depletion
iii. Hypoaldosteronism
iv. K^+-sparing diuretics
v. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers
vi. Trimethoprim

2. Symptoms of hyperkalemia
    a. Muscle weakness or paralysis is caused by changes in neuromuscular conduction; it typically occurs when plasma potassium exceeds 8 mEq/L.
    b. Abnormal cardiac conduction can first manifest as peaked, narrowed T waves (typically, when plasma potassium exceeds 6 mEq/L) and widening of the QRS, and it can progress to ventricular fibrillation and asystole.
    c. Not all patients will experience ECG changes, and the initial manifestation of hyperkalemia can be ventricular fibrillation; thus, consider emergency treatment even in patients with no ECG changes if plasma potassium exceeds 6.5 mEq/L.
    d. Conduction disturbances are increased by hypocalcemia, hyponatremia, acidosis, and rapid elevation in the plasma potassium concentration.
3. Pseudohyperkalemia should be considered if there is no apparent cause or symptoms of hyperkalemia.
    a. Can occur if K^+ is released from cells while or after obtaining the blood specimen, usually because of trauma during venipuncture (hemolysis)
    b. Can result from measurement of the serum rather than the plasma potassium concentration; caused by K^+ release during coagulation
    c. Contamination of blood specimen with potassium-containing intravenous fluids or parenteral nutrition
4. Treatment of hyperkalemia
    a. Patients with an asymptomatic elevation in the plasma potassium who do not have signs or symptoms can be treated with a cation exchange resin (e.g., sodium polystyrene sulfonate) alone.
    b. Urgent and immediate treatment is required for patients with the following signs or symptoms:
        i. Plasma potassium greater than 6.5 mEq/L
        ii. Severe muscle weakness
        iii. ECG changes
    c. Calcium should be administered intravenously to patients with symptomatic hyperkalemia to prevent hyperkalemia-induced arrhythmias, even if patients demonstrate normocalcemia.
        i. Calcium gluconate can be administered peripherally, and it is preferred to calcium chloride because of a reduced risk of tissue necrosis; dose is 10 mL (equivalent to 1 g, 90 mg elemental, or 4.65 mEq) of 10% calcium gluconate administered over 2–10 minutes. It can be repeated in 5 minutes if no improvement in ECG. Calcium chloride can be used if central intravenous access is available; however, the dose should be adjusted because 10 mL (1 g, 270 mg elemental, or 13.6 mEq) provides 3-fold the amount of elemental Ca as calcium gluconate.
        ii. Onset is within minutes, but duration is short (30–60 minutes).
        iii. It does not reduce plasma potassium, but it antagonizes the effect of K^+ in cardiac conduction cells
        iv. Use in urgent circumstances while waiting for other measures (e.g., insulin and glucose) to lower plasma potassium.
        v. Use caution in patients receiving digoxin because hypercalcemia can precipitate digoxin toxicity, and there are reports of sudden death.
    d. The following treatment options are transient, causing a temporary shift of K^+ from the EC fluid into the cells, and should be used for symptomatic hyperkalemia.
        i. Insulin and glucose
            (a) Dose is regular insulin 10 units intravenously plus 25–50 g of dextrose administered as a 50% dextrose intravenous push to prevent hypoglycemia.
            (b) Typically lowers plasma potassium by 0.5–1.5 mEq/L within 1 hour and may last for several hours
            (c) If patients have hyperglycemia, insulin alone can be administered.

(d) More predictable than sodium bicarbonate or β_2-adrenergic agonists in patients with kidney failure
(e) Caution with increased risk of insulin errors when used in emergencies (e.g., incorrectly preparing insulin infusions). Errors involving calculations (100 units/mL) and use of 5- or 10-mL syringes instead of an insulin syringe are possible.
(f) Monitor for signs and symptoms of hypoglycemia even if dextrose is given

ii. Sodium bicarbonate
(a) Dose is 50 mEq of intravenous sodium bicarbonate infused slowly over 5 minutes; it can be repeated after 30 minutes if needed.
(b) It can lower plasma potassium within 30–60 minutes and persist for several hours.
(c) The efficacy of bicarbonate is disputed, and it seems least effective in patients with advanced kidney disease; it may be effective in patients with underlying metabolic acidosis. Sodium bicarbonate use has recently been limited by shortages. Its use should be reserved for other conditions during shortages.

iii. β_2-Adrenergic agonists (e.g., albuterol)
(a) Dose is albuterol 10–20 mg nebulized over 10 minutes or 0.5 mg intravenously (not available in the United States).
(b) The dose will lower plasma potassium by 0.5–1.5 mEq/L.
(c) Onset is within 30 minutes with inhalation.
(d) Avoid use in patients with coronary ischemia because of the risk of tachycardia.
(e) Up to 40% of patients do not respond to inhaled albuterol (especially patients taking β-blockers); therefore, it is not recommended as a single agent for urgent treatment of hyperkalemia. Consider use in combination with insulin.

e. The previous treatment options should be followed by one of the following agents to remove excess K^+ from the body.
i. Diuretics
(a) Loop or thiazide-type diuretics increase K^+ renal excretion.
(b) Ineffective in patients with advanced kidney disease

ii. Cation exchange resins
(a) Sodium polystyrene sulfonate exchanges Na^+ for K^+, resulting in GI excretion of K^+. Exercise caution in patients with kidney disease or heart failure caused by Na^+ (and subsequent fluid) retention.
(b) Because of its slow onset (2 hours) and unpredictable efficacy, sodium polystyrene sulfonate is not indicated for emergency treatment of hyperkalemia.
(c) It was approved by the U.S. Food and Drug Administration in 1958, before demonstrated efficacy was required. No controlled trials show efficacy.
(d) Oral dose of sodium polystyrene sulfonate is 15 g repeated every 6 hours as needed. This can be mixed in 20–100 mL of water or syrup, but it is no longer recommended to mix in 70% sorbitol because of the risk of intestinal necrosis (there are also reports with the premixed 33% sorbitol suspension, but 70% sorbitol appears to have a stronger correlation with intestinal necrosis). Bowel injury is linked to the deposition of drug crystals in the GI tract. Oral sorbitol can prevent constipation associated with the resin; however, the highest risk of intestinal necrosis occurs when administered to patients within 1 week of surgery (occurs in about 1.8% of patients).
(e) Although the oral route is more effective, 30–50 g can also be given as a retention enema mixed in 100–200 mL of an aqueous vehicle (e.g., water, 10% dextrose) that has been warmed to body temperature and kept in the colon for 30–60 minutes, or up to 3 hours. Irrigate the colon afterward. Sorbitol is not recommended as a vehicle for rectal use because of the risk of intestinal necrosis and other serious GI adverse events.

(f) A systematic review found that GI injury is also associated with sodium polystyrene preparations without sorbitol (Am J Med 2013;126:264).

(g) Two potassium binders have recently been approved for use in hyperkalemia. As opposed to sodium polystyrene sulfonate, patiromer exchanges Ca^{2+} for K^+, resulting in GI excretion of K^+. As with other binders, caution should be used if patiromer is administered with other medications because it may reduce their absorption. Like sodium polystyrene sulfonate, patiromer should not be used for life-threatening hyperkalemia, because it has a slower onset of action. The other potassium-binding agent, sodium zirconium cyclosilicate, works by exchanging potassium for hydrogen and sodium.

iii. Dialysis

(a) It is used when other measures are ineffective or when severe hyperkalemia is present.

(b) Plasma potassium falls by more than 1 mEq/L in the first hour of dialysis and by about 2 mEq/L after 3 hours of dialysis.

(c) Hemodialysis removes K^+ faster than peritoneal dialysis.

(d) Monitor for rebound increase in K^+ after dialysis.

(e) It is used in patients with advanced kidney disease

Patient Case

7. A 61-year-old man comes to the emergency department with shortness of breath and bilateral lower leg edema. Pertinent vital signs and laboratory values include heart rate 30 beats/minute, blood pressure 102/57 mm Hg, K^+ 7.9 mEq/L, Na^+ 139 mEq/L, glucose 228 mg/dL, Ca^{2+} 8.8 mg/dL, digoxin 2.2 ng/mL, BUN 49 mg/dL, and SCr 2.4 mg/dL. His ECG shows wide QRS and peaked T waves. His medical history includes heart failure, atrial fibrillation, coronary artery disease, peripheral arterial disease, and diabetes. The patient has peripheral intravenous access and an external pacemaker. Which treatment is most appropriate?

A. Calcium gluconate 10 mL intravenously over 2 minutes.

B. Insulin 10 units intravenously.

C. Sodium bicarbonate 50 mEq intravenously over 10 minutes.

D. Albuterol 10 mg nebulized over 10 minutes.

VIII. DISORDERS OF MAGNESIUM HOMEOSTASIS

A. Normal serum magnesium concentration is 1.7–2.3 mg/dL (1.4–1.8 mEq/L or 0.85–1.15 mmol/L).

B. Hypomagnesemia (serum magnesium concentration less than 1.7 mg/dL)

1. Usually associated with impaired intestinal absorption (e.g., ulcerative colitis, diarrhea, pancreatitis, chronic laxative abuse), inadequate intake, hypokalemia, or increased renal excretion (e.g., diuretic use)
   a. Common in hospitalized patients
   b. Often associated with alcoholism and delirium tremens
2. Often occurs concurrently with hypokalemia and hypocalcemia
3. Signs and symptoms
   a. Neuromuscular symptoms include tetany, twitching, and seizures.
   b. Cardiovascular symptoms include arrhythmias, sudden cardiac death, and hypertension.
4. Treatment
   a. Oral supplements (e.g., magnesium oxide, magnesium-containing antacids or laxatives) can be used for asymptomatic patients; however, treatment is limited by the high frequency of diarrhea.

b. Symptomatic patients should initially be treated with 1–4 g (8–32 mEq) of magnesium sulfate by slow intravenous infusion (about 1 g/hour to avoid hypotension or increased renal excretion because of rapid administration). Initial boluses can be followed by about 0.5 mEq/kg/day added to intravenous fluid and administered as a continuous infusion. For emergency treatment (e.g., torsades), magnesium can be administered by intravenous push. Asymptomatic patients with mild to moderate hypomagnesemia should also be treated with 1–4 g of magnesium sulfate by slow intravenous infusion.
c. Reduce the dose by half in patients with kidney insufficiency.
d. About half of administered magnesium is excreted in the urine; therefore, magnesium replacement can occur over 3–5 days.
e. Intravenous magnesium has also been affected by shortages. Reserve use for symptomatic patients.

C. Hypermagnesemia (serum magnesium greater than 2.3 mg/dL)
1. Rarely occurs and is generally associated with chronic kidney disease
2. Signs and symptoms include nausea, vomiting, bradycardia, hypotension, heart block, asystole, respiratory failure, and death; signs and symptoms rarely occur unless magnesium concentration is greater than 4–5 mg/dL.
3. Treatment
a. Discontinue all magnesium-containing medications.
b. Asymptomatic patients with normal kidney function can be treated with 0.9% sodium chloride and loop diuretics.
c. Symptomatic patients should be treated with 100–200 mg of elemental Ca^{2+} administered intravenously over 5–10 minutes for cardiac stability.
d. Hemodialysis may be needed for patients with kidney disease.

IX. DISORDERS OF PHOSPHORUS HOMEOSTASIS

A. Normal serum phosphorus concentration is 2.5–4.5 mg/dL.

B. Hypophosphatemia (serum phosphorus concentration less than 2.5 mg/dL)
1. Causes of hypophosphatemia
a. Increased renal elimination (e.g., diuretics, glucocorticoids, sodium bicarbonate)
b. Rapidly refeeding patients with chronic malnutrition (see "refeeding syndrome" in Parenteral Nutrition section)
c. Respiratory alkalosis
d. Treatment of diabetic ketoacidosis; phosphorus shifts into the IC compartment as diabetic ketoacidosis is corrected
2. Signs and symptoms
a. Tissue hypoxia can occur because of a decrease in oxygen release to peripheral tissues.
b. Neurologic manifestations include confusion, delirium, seizures, and coma.
c. Pulmonary and cardiac symptoms can include respiratory failure, difficulty weaning from mechanical ventilation, heart failure, and arrhythmias.
d. Other organ systems affected include muscle, hematologic, bone, and kidney.
3. Prevention and treatment
a. Prevent hypophosphatemia by supplementing intravenous fluid with 10–30 mmol/L intravenous phosphorus in patients at risk of hypophosphatemia (e.g., malnourished, alcoholism, diabetic ketoacidosis).

b. Oral phosphorus products (e.g., K-Phos Neutral; also contain K^+ and Na) can be used for asymptomatic patients, but they are poorly absorbed.
c. Symptomatic patients typically receive 15–30 mmol and sometimes up to 60 mmol (or 0.5–0.75 mmol/kg of IBW) of phosphorus (sodium phosphate or potassium phosphate) administered intravenously over 3–6 hours (maximum rate is 7.5 mmol/hour). Note Na^+ content (4 mEq per 3 mmol of phosphate) and K^+ content (4.4 mEq per 3 mmol of phosphate).

4. Phosphate shortages
   a. Reserve phosphate products for patients who need them most (e.g., children, neonates, diabetic ketoacidosis, refeeding syndrome, critically ill patients).
   b. Intravenous fat emulsions contain 15 mmol/L as egg phospholipids; this may be sufficient phosphate for some patients.

C. Hyperphosphatemia
1. It typically occurs in patients with chronic kidney disease or hypoparathyroidism.
2. In general, patients are asymptomatic, but they can have signs and symptoms including hypocalcemia, ECG changes, paresthesias, and vascular calcifications.
3. For treatment, see Treatment of Hyperphosphatemia in the Nephrology chapter.

X. DISORDERS OF CALCIUM HOMEOSTASIS

A. Normal serum calcium concentration is 8.5–10.5 mg/dL (total Ca^{2+} includes bound and unbound Ca^{2+}), and normal ionized calcium is 1.1–1.3 mmol/L (or 4.4–5.3 mg/dL).

B. Distribution of Ca^{2+}
1. EC fluid contains less than 1% of the total body stores of Ca^{2+}; 99% of total body stores of Ca^{2+} are in skeletal bone.
   a. About half of Ca^{2+} in the EC compartment is bound to plasma proteins (primarily albumin).
   b. The active form of Ca^{2+} is the unbound or ionized Ca^{2+}.
2. Ionized Ca^{2+} is regulated by parathyroid hormone, phosphorus, vitamin D, and calcitonin.

C. Hypocalcemia
1. It occurs in patients with chronic kidney disease, hypoparathyroidism, vitamin D deficiency, alcoholism, and hyperphosphatemia, and in patients receiving large amounts of blood products or patients undergoing continuous renal replacement therapy (CRRT [i.e., Ca^{2+} chelates with citrate used as anticoagulation in blood products or for plasmapheresis or CRRT.])
2. Factors that cause an increase in EC Ca^{2+} binding to albumin (e.g., metabolic alkalosis) can cause a reduction in plasma ionized Ca^{2+} concentration, leading to symptomatic hypocalcemia.
3. A low serum albumin will cause a falsely low total serum calcium reading; therefore, an adjustment is necessary. Subtract a patient's serum albumin from a normal serum albumin of 4 g/dL, multiply by 0.8 mg/dL, and then add to the total serum calcium concentration to correct the value. An ionized calcium level may be a more accurate measure of calcium in critically ill patients.
4. Signs and symptoms include tetany, muscle spasms, hypoactive reflexes, anxiety, hallucinations, lethargy, hypotension, and seizures.
5. Treatment
   a. Asymptomatic hypocalcemia associated with hypoalbuminemia is typically associated with normal ionized Ca^{2+} concentrations and therefore does not require treatment.

b. Asymptomatic hypocalcemia can be treated with oral Ca^{2+} supplements at a dose of 2–4 g/day of elemental Ca^{2+} in divided doses; patients may also require vitamin D supplementation.
c. Symptomatic hypocalcemia is treated with 200–300 mg of elemental Ca^{2+} administered intravenously over 5–10 minutes; this is sometimes followed by a continuous infusion.
    i. Equivalent to 1 g of calcium chloride (273 mg of elemental Ca^{2+}) administered through a central intravenous catheter; peripheral administration of calcium chloride can result in severe limb ischemia
    ii. Equivalent to 2–3 g of calcium gluconate (180–270 mg of elemental Ca^{2+}); preferred for peripheral intravenous administration
    iii. Do not infuse Ca^{2+} at a rate faster than 60 mg of elemental Ca^{2+} per minute; rapid administration, which is not recommended, is associated with hypotension, bradycardia, or asystole.
    iv. The duration of an intravenous dose of Ca^{2+} is ideally 1–2 hours. If a continuous infusion is used, the rate should be 0.5–2 mg/kg/hour of elemental Ca^{2+}.

6. Calcium shortages
    a. If there is a shortage of calcium gluconate, do not add calcium chloride to PN. Use multielectrolyte products in PN, if possible.
    b. The safety of diluted calcium chloride administered peripherally is unknown.

D. Hypercalcemia (serum calcium concentration greater than 10.5 mg/dL) is usually related to malignancy or hyperparathyroidism; see the chapters on Oncology Supportive Care and Nephrology.

XI. ENTERAL NUTRITION

A. Indication and timing: EN is used in patients who are at risk of malnutrition and in whom it is anticipated that oral feedings will be inadequate for 5–7 days. Malnutrition is associated with poor wound healing and increased risk of infection. According to the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, well-nourished adults without excessive metabolic stress can usually tolerate little to no nutrition for up to 7 days. The 2016 ASPEN and Society of Critical Care Medicine (SCCM) guidelines for critically ill patients recommend starting enteral feeding within the first 24–48 hours after intensive care unit admission.

B. EN contraindications
1. Complete intestinal obstruction
2. GI fistula (if a feeding tube cannot be placed distal to the fistula or if high-output fistula, which is defined as greater than 500 mL of output per day)
3. Extremely short bowel
4. Severe diarrhea or vomiting
5. Hemodynamic instability or intestinal ischemia
6. Paralytic ileus (however, many patients can be fed through the small bowel, despite an ileus)
7. Absence of bowel sounds is not a contraindication for the provision of EN (i.e., positive bowel sounds are not required for EN initiation), which promotes gut motility

C. EN administration routes
1. Large-bore orogastric and NG tubes
    a. NG tubes are the most common tubes for short-term enteral access.
    b. Orogastric tubes are preferred in patients with nasal or facial trauma or sinusitis, but they are uncomfortable for alert patients.

c. These tubes can be used for stomach decompression in addition to feeding.
d. Prolonged use can cause sinusitis or nasal mucosal ulceration.
e. Patients with a gastric ileus will not tolerate NG feedings, and there is an increased risk of aspiration.

2. Small-bore feeding tubes
   a. These tubes are most commonly placed through the nose, but they can also be placed orally in patients with nasal or facial trauma or sinusitis
   b. They can be placed with the feeding tube tip terminating in the stomach, but because they are smaller and more flexible than NG tubes, they can also be placed past the pyloric sphincter to improve tube feeding tolerance and prevent aspiration.
   c. Nasoduodenal tubes are also smaller than NG tubes, and they can clog from crushed medications if they are not flushed appropriately. Nasojejunal tubes are advanced into the fourth portion of the duodenum or past the ligament of Treitz.
   d. Patients with a gastric ileus or gastroparesis may tolerate feeding by the nasoduodenal or nasojejunal route.
3. Percutaneous endoscopic gastrostomy tubes are placed through the abdominal wall into the stomach for patients requiring long-term feeding; jejunostomy tubes are placed through the abdominal wall into the jejunum, usually to facilitate immediate postoperative or postinjury feeding

D. EN delivery
1. Gravity control refers to delivery with tubing that is fitted with a roller clamp to allow infusion into the stomach as desired.
2. Continuous infusion by an enteral feeding pump is usually used in hospitals because of the lower risk of aspiration compared with bolus feedings; it must be used for duodenal or jejunal feedings.
3. Cyclic feedings are administered continuously for 10–12 hours (overnight) to facilitate patient mobility during the daytime.
4. Intermittent bolus feedings of 100–300 mL for 30–60 minutes every 4–6 hours can be used only for feeding tubes ending in the stomach in stable patients.

E. Benefit of EN
1. EN is preferred in patients with a functional GI tract because it is associated with a lower risk of infection than PN. Early administration of EN is associated with lower rates of infection and shorter lengths of stay.
2. GI mucosal atrophy occurs with an absence of EN or oral nutrition. This can increase the risk of bacterial translocation because of gut bacteria crossing the weakened intestinal barrier.

F. EN formulations
1. Formulations typically contain carbohydrate, fat, protein, electrolytes, water, vitamins, and trace elements in varying amounts.
2. Intact or polymeric formulas are used in patients with normal digestive processes, and they typically contain 1–1.2 kcal/mL.
   a. These are generally inexpensive and an appropriate first choice for many patients.
   b. Some polymeric formulas are concentrated for patients requiring fluid restriction and contain 2 kcal/mL.
   c. Some polymeric formulas are designed for oral administration and are used to supplement the patient's diet.
3. Elemental or semi-elemental formulas are easily digested by patients with impaired digestive capacity or malabsorption (e.g., short bowel, pancreatic insufficiency); they are typically more expensive than polymeric EN.

4. Some EN contains fiber for patients with constipation. Examples include Replete with Fiber and Jevity.
5. Disease-specific EN
    a. EN formulations for patients with renal failure are typically concentrated (i.e., 2 kcal/mL to adhere to fluid restrictions) and can contain differing amounts of protein and electrolytes.
    b. Some EN products designed for patients with respiratory failure have more calories from fat (40%–55% of total calories) and fewer from carbohydrates to reduce the production of CO_2 and facilitate ventilator weaning. However, excessive CO_2 production is caused primarily by overfeeding with total calories rather than the total amount of carbohydrates; therefore, these more expensive formulations may be unnecessary as long as the patient is not being overfed.
    c. EN formulations for patients with diabetes have more calories from fat, fewer calories from carbohydrates, and added fiber to improve glycemic control.
    d. EN formulations for patients with hepatic failure and hepatic encephalopathy contain more branched-chain AAs and fewer aromatic AAs, which may improve encephalopathy (controversial), but are not commonly used.
    e. EN for highly stressed patients (e.g., trauma, burn injury, acute respiratory distress syndrome, sepsis) is enhanced with protein, arginine, glutamine, omega-3 fatty acids, nucleotides, or beta-carotene. These enteral formulations are designed to improve immune function and clinical outcomes. Immune-modulating formulas are recommended for surgical ICU patients in the postoperative setting, but are not recommended for the medical ICU population.
    f. Specialty formulas are not recommended for routine use in a general ICU setting.

G. EN complications
    1. Improper tube placement or displacement
    2. Clogged feeding tubes
        a. Prevent by flushing feeding tube before, between, and after the administration of each drug. The use of liquid formulations of medications, if available, is also recommended.
        b. Unclog feeding tubes with warm water or a pancreatic enzyme solution mixed with oral sodium bicarbonate. Avoid using cola or juice.
    3. Aspiration
        a. Prevent by keeping the head of bed elevated at 30–45 degrees.
        b. Prevent delays in gastric emptying using an EN formula with less fat. Gastric motility can be increased with metoclopramide (5–10 mg intravenously every 6 hours) or erythromycin (250 mg intravenously every 6–8 hours administered until tolerating EN for at least 24 hours). Metoclopramide and erythromycin can be combined, but monitor for diarrhea and tachyphylaxis. Avoid prolonged use of promotility agents because of increased risk of adverse effects.
        c. Administering EN by a feeding tube with the tip terminating beyond the pyloric sphincter can prevent aspiration pneumonia.
        d. Prevent also by initiating EN at a slow rate (e.g., 20 mL/hour) and advance every 4–6 hours as tolerated to goal rate.
    4. Diarrhea
        a. It is more common with products with a higher osmolarity.
        b. Consider other causes of diarrhea such as antibiotic use, infection, lactose intolerance, magnesium, and sorbitol in liquid medication preparations.
    5. Constipation can be prevented by adding fiber or bowel stimulation.
    6. Dehydration

7. Hypernatremia occurring when patients are given insufficient water while receiving EN
    a. Patients require about 30 mL/kg/day of water.
    b. Hypernatremia typically occurs in patients with altered mental status who may be unable to communicate thirst.
    c. Calorie-dense (i.e., 1.5 or 2 kcal/mL) EN formulas have less water than products containing 1 kcal/mL; therefore, additional water is needed to prevent hypernatremia.
8. Nasopharyngeal erosions, epistaxis, tracheoesophageal fistula
9. Sinusitis
10. Electrolyte abnormalities most likely to occur in patients who develop refeeding syndrome (discussed later)

Patient Case

8. A 72-year-old woman (weight 65 kg) is switched from a standard enteral formula to a concentrated tube feeding designed for patients with kidney disease, because of hyperkalemia. The patient's baseline and current SCr is 1.7 mg/dL, and her urine output is about 50 mL/hour. The tube feeding is infusing at a goal rate of 35 mL/hour through an NG feeding tube providing 2 kcal/mL, Na^+ 41 mEq/L, and 717 mL/L of water. The patient's serum sodium was 140 mEq/L when the tube feeding was initiated a few days ago, and her Na^+ is now 145 mEq/L. What is the best approach for preventing hypernatremia in this patient?

    A. Change to an EN formula with a lower concentration of Na^+.

    B. Administer intravenous D_5W at 45 mL/hour.

    C. Administer 200 mL of water through a feeding tube every 4 hours.

    D. Reduce the tube feeding to 30 mL/hour.

H. EN monitoring
    1. Blood glucose concentration
    2. Head of bed elevation to 30–45 degrees
    3. GI tolerance
        a. Abdominal pain or distension
        b. Stool frequency and volume
        c. Nausea, vomiting, and diarrhea
        d. Checking gastric residuals is not recommended
    4. Prealbumin weekly (exception: Caution in critically ill patients because it reflects acute-phase response rather than nutritional status); see goals in the Parenteral Nutrition section.
    5. Serum sodium and other electrolytes
    6. Wound healing a sign of adequate nutritional therapy
    7. Other medications that add additional calories (e.g., propofol, clevidipine) that require EN rates to be adjusted

I. Developing an EN Regimen (Table 9)

Table 9. Developing an EN Regimen

Steps	Calculation Guide	Example
Determine caloric requirements	25–35 kcal/kg/day *or* estimate energy requirements using an equation such as the Harris-Benedict equation (see more details in Parenteral Nutrition section and Critical Care chapter)	A 60-kg patient would require about 25 kcal/kg/day × 60 kg = 1500 kcal
Choose a formula and assess the calories per milliliter	Usually 1, 1.2, 1.5, or 2 kcal/mL	Choose a 1-kcal/mL formula
Determine infusion rate	(Volume of EN)/24 hr	1500 mL/24 hr = 62.5 mL/hr
Ensure that patient will receive sufficient protein	See product information to find protein content (see protein requirements in Parenteral Nutrition section)	Replete with Fiber provides 64 g/L of protein; therefore, 1500 mL will provide 96 g of protein, or 1.6 g/kg for a patient weighing 60 kg
Ensure that the patient will receive about 30 mL/kg/day of water	See product information to find water content	Replete with Fiber provides 832 mL/L of free water. A patient receiving 1500 mL/day would need about 250 mL of additional water, which can be administered as water flushes through the feeding tube (i.e., 60–70 mL every 6 hr); it is important to consider other fluids that the patient may be receiving

EN = enteral nutrition.

J. Drug administration using enteral access
   1. Liquids are preferable, and they should be diluted with 2–3 times the medication volume with water to decrease osmolality.
   2. Diarrhea can occur with medications having a high osmolality (e.g., medications mixed in sorbitol).
   3. Flush with 20 mL of water before and after each drug administered.
   4. Do not crush sustained-release or enteric-coated pills.
   5. Mix crushed tablets or capsule contents with 10–15 mL of water and administer each drug separately.
   6. It may be necessary to discontinue tube feedings before and after drug administration temporarily to prevent reduced bioavailability (e.g., fluoroquinolones, phenytoin, warfarin, bisphosphonates).
   7. Consider feeding tube location and subsequent drug absorption (e.g., for efficacy; antacids need to be administered into the stomach, not the duodenum).

XII. PARENTERAL NUTRITION

A. Parenteral nutrition (PN) is the administration of intravenous nutrition in patients with a nonfunctioning or inaccessible GI tract in which the duration of PN is anticipated to be at least 7 days (i.e., it is anticipated that the patient will be unable to be fed orally or enterally for at least 7 days). In patients who are at high nutritional risk or severely malnourished and cannot tolerate EN, PN should be initiated as soon as possible.

B. Indications for PN
   1. Severe pancreatitis in patients who cannot tolerate EN
   2. Peritonitis
   3. Severe inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis)
   4. Extensive bowel resection (e.g., short bowel syndrome) causing malabsorption or maldigestion
   5. Complete bowel obstruction
   6. Severe intractable vomiting or diarrhea
   7. Inability to meet full nutritional needs by enteral route alone (can use PN as supplement to EN)

C. Intravenous infusion of PN (Table 10)

Table 10. Estimating the Osmolarity of PN for 1 L of Solution

Nutrient	Estimated Osmolarity
Amino acids	10 mOsm/g
Dextrose	5 mOsm/g
Lipid emulsion 10%–20%	1.3–1.5 mOsm/g
Sodium chloride/acetate	2 mOsm/mEq
Potassium chloride/acetate	2 mOsm/mEq
Calcium gluconate	0.68 mOsm/mL
Magnesium sulfate	4.06 mOsm/mL

PN = parenteral nutrition.

1. PN should be administered through a central line. This includes any intravenous catheter (e.g., peripherally inserted central catheter, Hickman, Port-A-Cath) where the tip of the catheter is in the superior vena cava or adjacent to the right atrium (femoral catheters should be avoided because of higher risk of venous thrombosis and catheter-related infection).
2. Peripheral access, which also includes midline catheters, is defined as the catheter tip position outside the central vessels or inferior or superior vena cava. If a peripheral vein is used for PN administration, the osmolarity must not exceed 900 mOsm/L. Peripheral administration can be used in patients with an appropriate indication for PN (see Indications for PN above) when central intravenous access is unavailable and the need for PN is expected to be less than 2 weeks.
   a. Final dextrose concentration should be 10% or less.
   b. Final AA concentration should be 2.5%–4%.
   c. Ca^{2+} concentration should be 5 mEq/L or less.
   d. K^{+} concentration should be 40–60 mEq/L or less.

3. In hospitalized patients, PN is typically administered as a continuous infusion, which is infused over 24 hours.
4. Ambulatory patients may prefer a cyclic PN in which the PN is usually infused for 12 hours.
5. Infusions are generally better tolerated by patients if they are removed from the refrigerator and allowed to come to room temperature before infusion.

D. Types of PN admixtures (Table 11)

Table 11. 2-in-1 PN Compared with 3-in-1 PN

	Advantages	Disadvantages
2-in-1	Longer stability Visual inspection easier Filter using 0.22-micron filter (bacteria-eliminating) Lipids require 1.2-micron filter	Increased nursing time Requires two sets of tubing and infusion pumps Increased bacterial growth in lipids Maximum 12-hr hang time of separate lipids
3-in-1	Time efficient for nurses Single bag with single tube and infusion pump Decreased vein irritation Inhibited bacterial growth	Shorter stability (1–2 days) Complex compounding (without automated compounder) Visual inspection difficult Emulsion instability Must use 1.2-micron filter, not 0.22-micron Limited compatibility with medications Catheter occlusion more common

1. 2-in-1 refers to PN in which all nutrients are mixed in the same intravenous bag, except for lipids, which are administered by a separate infusion.
   a. Lipids are infused separately, no faster than 0.1 g/kg/hour in adults, using a 1.2-micron filter
   b. Rapid administration of lipids is associated with headache, fever, nausea, hypertriglyceridemia, dyspnea, cyanosis, flushing, sweating, and back or chest pain.
   c. Lipid infusion time should be less than 12 hours because of the potential for microbial growth after this time (growth is reduced when lipids are mixed with dextrose and AAs, as in the 3-in-1 described below, because of reduced pH and increased osmolarity).
   d. Administration tubing for a 2-in-1 should be changed every 24 hours; lipid tubing should be discarded after use (no longer than 12 hours).
2. 3-in-1 (also called *total nutrient admixture*) refers to PN in which all nutrients are mixed in the same intravenous bag.
   a. The stability of a 3-in-1 depends on the pH, which is determined primarily by the final AA concentration (maintain at least 4%).
   b. Do not add concentrated dextrose directly to a lipid emulsion when mixing (see order of mixing discussed later).
   c. Avoid excessive amounts of Ca^{2+} and magnesium (see recommended doses).
   d. Administration tubing for a 3-in-1 should be changed every 24 hours.
   e. Total nutrient admixtures should have a final concentration of amino acids ≥ 4%, monohydrated dextrose ≥ 10%, and injectable lipid emulsion ≥ 2%.

E. Premixed PN
   1. Products available in the United States
      a. Clinimix is a two-compartment bag containing AAs in one compartment and dextrose in the other. This product is available with and without electrolytes. The seal between the two-compartment bag must be broken to mix the AAs and dextrose. Lipids can be added to the container after compartments are mixed or can be administered by Y-site.
      b. ProcalAmine is a solution containing 3% AAs, glycerin (4.3 kcal/g), and electrolytes in a single container, but it is not sufficient for most patients because of insufficient protein and calories.
      c. Kabiven, a newer solution, contains AAs, electrolytes, dextrose, and a lipid emulsion. It is available in a 3-compartment bag for central line administration only. Perikabiven is also available for use for peripheral and central administration.
   2. Patient selection
      a. Evidence is insufficient to show that customized PN is superior to standardized premixed products.
      b. Consider in stable patients who require PN.
      c. Avoid in patients with fluid restriction or high protein needs.
   3. Premixed products require fewer manipulations and have a lower risk of contamination and compounding errors, but they may still require additives (e.g., electrolytes, vitamins, trace elements).

F. Nutritional components of PN formulation
   1. Dextrose used for compounding PN is usually 70%, and it contains 3.4 kcal/g. Glycerol (or glycerin) is another carbohydrate source. Glycerol provides 4.3 kcal/g, and it is used in premixed parenteral products.
   2. Fat emulsion is available as 10% or 20% and contains about 10 kcal/g; it is also available as a 30% formulation for compounding in 3-in-1 only. Smoflipid was recently approved as 20%; it contains soybean oil, medium chain triglycerides, olive oil, and fish oil. Omegaven 10% was also recently approved for use in the United States. Intralipid is available as a 20% solution.
   3. AAs are available as 3%–20% and provide 4 kcal/g.
   4. Electrolytes are added to maintain physiologic serum concentrations.
   5. Multivitamins and trace elements are added on the basis of the recommended daily amount.

G. Developing a PN regimen for administration through a central intravenous line
   1. Determine caloric requirements.
      a. For patients with a body mass index (BMI) less than 30 kg/m^2, administer 25–35 kcal/kg/day based on actual body weight [BMI = (Weight in kg)/(Height in meters)^2].
      b. If BMI exceeds 30 kg/m^2, can administer 11–14 kcal/kg based on actual body weight or 22–25 kcal/kg based on IBW.
         i. Alternatively, some practitioners advocate using adjusted body weight (ABW) rather than IBW.
         ii. ABW = [(actual weight – IBW) × 0.25] + IBW.
      c. Hypocaloric feeding with high protein in EN and PN involves the administration of about 80% of caloric requirements, and it can be considered in patients with obesity (except in patients with kidney failure requiring hemodialysis and patients with hepatic failure; these patients have increased protein and caloric requirements to maintain a positive nitrogen balance).

   d. One method is to estimate basal energy expenditure (BEE) using the Harris-Benedict equation:
      i. Men: BEE = 66 + 13.7(Weight in kg) + 5(Height in cm) – 6.8(Age in years).
      ii. Women: BEE = 655 + 9.6(Weight in kg) + 1.8(Height in cm) – 4.7(Age in years).
   e. Energy expenditure can also be estimated through indirect calorimetry in critically ill patients (see the Critical Care chapter).
2. Determine fluid requirements.
   a. Usually 30–35 mL/kg/day or 2500–3500 mL/day (for patients without fluid restrictions) to maintain urine output in the range of 0.5–2 mL/kg/hour
   b. Fluid requirements for patients with fluid restrictions (e.g., kidney or cardiac dysfunction) should be individualized.
   c. Do not use PN for fluid replacement but for maintenance fluid only.
3. Determine protein (AA) requirements.
   a. For patients with a BMI less than 30 kg/m^2, protein is usually in the range of 0.8–2 g/kg/day on the basis of actual body weight (may be higher in burn or trauma patients).
      i. Maintenance 0.8–1 g/kg/day
      ii. Moderate stress 1.3–1.5 g/kg/day
      iii. Severe stress 1.5–2 g/kg/day
   b. For patients with a BMI of 30–40 kg/m^2, can give protein 2 g/kg/day based on IBW. For patients with a BMI greater than 40 kg/m^2, can give 2.5 g/kg/day based on IBW.
   c. Patients with chronic kidney dysfunction may need protein restriction to prevent uremia.
      i. Kidney dysfunction without dialysis, 1 g/kg/day
      ii. Kidney failure with intermittent hemodialysis, 1.2–1.5 g/kg/day (1.5–2.5 g/kg/day if continuous renal replacement)
   d. Calories from protein (4 kcal/g) should be included in the total caloric provisions to prevent overfeeding.
   e. For 3-in-1 formulations, the final AA concentration should be around 4% to provide adequate buffering capacity and prevent lipid emulsion destabilization.
   f. Complete protein requirements can be provided on day 1 of PN (i.e., there is no need to slowly titrate up to recommended amount).
4. Calculate remaining nonprotein calories and administer about 20%–30% of total calories as lipid and the remainder as dextrose.
   a. Make sure dextrose rate of administration does not exceed the maximum rate of hepatic oxidation rate of 4–5 mg/kg/minute (may be lower in critically ill patients, so monitor for hyperglycemia and adjust amount of dextrose provided if needed).
      i. Initial dextrose amounts can be in the range of 150–200 g/day.
      ii. May need to reduce to 100–150 g/day initially in patients with diabetes or stress-induced hyperglycemia; increase gradually during first 3–4 days to goals if blood glucose values are less than 140–180 mg/dL.
   b. A higher percentage of calories from lipid (up to 50%–60%, or 2.5 g/kg/day) can be provided for a short time in certain cases (e.g., hyperglycemia, hypercapnia).
   c. Essential fatty acid deficiency can be prevented by supplying approximately 2%–4% of total calories as lipid (can administer lipid emulsion once every 1–2 weeks).

5. Estimate a daily maintenance amount of electrolytes, vitamins, and trace elements (Box 5).

Box 5. Central PN calculations

Example of a central 3-in-1 PN formula for a 70-kg patient hospitalized with ischemic bowel:
1. Total calories estimated as 30 kcal/kg × 70 kg = 2100 kcal
2. Fluid requirements estimated as 1500 mL + (20 mL/kg × 50 kg) = 2500 mL/day
3. Estimated protein needs are 1.5 g/kg × 70 kg = 105 g of protein. 4 kcal/g × 105 g = 420 kcal from protein; using 10% AA-based solution, will need 1050 mL to equal 105 g of protein (can round to 1000 mL if this makes compounding easier)
4. Determine calories from fat and dextrose. Total calories needed is 2100 − 420 kcal from AAs = 1680 remaining non–protein calories needed. Administer 25%–30% of total kilocalories as lipid, or about 500 kcal from lipid. Using 20% lipid emulsion, 250 mL is needed to equal 500 kcal (about 2 kcal/mL) Total calories needed is 2100 kcal − 420 kcal (AA) − 500 kcal (lipid) = 1180 kcal needed from dextrose. Assuming 3.4 kcal/g, about 350 g dextrose will be needed. Using a 70% base dextrose solution, 500 mL will be needed to equal 350 g, or 1190 kcal. Calculate the rate of dextrose administration in milligrams per kilogram per minute: [(350 g/24 hr) × (1000 mg/g) × (1 hr/60 min)]/70 kg = 3.5 mg/kg/min. This is an appropriate rate of dextrose administration.
5. The final formula will contain the following: AA 10%, 1050 mL Lipid 20%, 250 mL Dextrose 70%, 500 mL Electrolytes, multivitamins, and trace elements (about 110 mL) Final volume of 1910 mL to infuse at 1910 mL over 24 hours = 80 mL/hr (Final volume assumes the patient is receiving about 350 mL of fluid from other medications to meet fluid requirements)
6. Final concentration of macronutrients in PN is: AA 105 g/1910 mL final volume = 5.5% Lipid 50 g/1910 mL = 2.6% Dextrose 350 g/1910 mL = 18%
7. Final caloric value of PN is: AA 105 g × 4 kcal/g = 420 kcal Lipid 50 g × 10 kcal/g = 500 kcal Dextrose 350 g × 3.4 kcal/g = 1190 kcal Total calories = 420 + 500 + 1190 = 2110 kcal/70 kg = 30 kcal/kg 24% of total calories are provided as lipid

AA = amino acid; PN = parenteral nutrition.

   a. Electrolyte abnormalities should be addressed and corrected before PN is initiated. Avoid replacing electrolyte deficiencies using PN in acutely ill patients.
   b. Maintenance electrolytes (amounts will vary and should be individualized)
      i. Sodium 60–150 mEq/day (1–2 mEq/kg/day)
      ii. K^+ 40–80 mEq/day (1 mEq/kg/day)
      iii. Phosphate 10–40 mmol/day (or 15 mmol/1000 kcal)
      iv. Ca^{2+} 10–15 mEq/day (gluconate is preferred to prevent incompatibilities)
      v. Magnesium 8–20 mEq/day (sulfate form is preferred to Cl to prevent incompatibilities)
      vi. Cl and acetate salt forms to maintain acid-base balance.

vii. Electrolyte adjustment
  (a) Typically, greater amounts of magnesium, phosphorus, and K^+ will be needed during the first few days of PN because of IC shifts.
  (b) Cl and acetate salt forms can be adjusted as needed to maintain acid-base balance (discussed under Monitoring Patients Who Are Receiving PN).

c. Standard trace elements containing selenium, chromium, copper, manganese, and zinc (e.g., MTE-5)
  i. Patients with high-output fistulas, diarrhea, burns, or large open wounds may require additional zinc supplementation.
  ii. Patients with chronic diarrhea, malabsorption, or short-gut syndrome or those with critical illness may require additional selenium supplementation.
  iii. Patients with severe cholestasis should have copper and manganese restricted to prevent accumulation and toxicity because both undergo biliary elimination.

d. Parenteral multivitamin added daily (generally contains 150 mcg of vitamin K).
  i. Additional thiamine (25–100 mg) can be supplemented in patients with a history of alcohol abuse.
  ii. During shortages of parenteral vitamins, can reduce frequency of administration to three times/week or can administer individual vitamins daily (i.e., thiamine, ascorbic acid, niacin, pyridoxine, folic acid) or monthly (i.e., vitamin B_{12})

H. Developing a PN regimen for administration through a peripheral intravenous line (Box 6)

Box 6. Peripheral PN Calculations

Example of a peripheral 3-in-1 PN formula for a 70-kg patient:
1. Total calories estimated as 30 kcal/kg × 70 kg = 2100 kcal
2. Fluid requirements estimated as 1500 mL + (20 mL/kg × 50 kg) = 2500 mL/day; prescriber wants PN to contain no more than 2000 mL
3. Calculate amount of dextrose as 2000 mL × 10% = 200 g of maximum dextrose recommended
4. Calculate amount of AA as 2000 mL × 3% = 60 g
5. Add about 500 kcal as lipid (can add more if patient tolerates).
6. Calculate volume so far. Using 70% dextrose, need 286 mL to equal 200 g of dextrose. Using 10% AA, will need 600 mL to equal 60 g. Using 20% lipid, will need 250 mL. Will add electrolytes, trace elements, multivitamins, and enough sterile water for a total volume of 2000 mL
7. Final formula will contain the following: AA 10% 600 mL Lipid 20% 250 mL Dextrose 70% 286 mL Electrolytes, multivitamins, and trace elements Sterile water added for 2000 mL final volume to infuse at 2000 mL/24 hr = 83 mL/hr
8. Final concentration of macronutrients in PN is: AA 60 g/2000 mL final volume = 3% Lipid 50 g/2000 mL = 2.5% Dextrose 200 g/2000 mL = 10%
9. Final caloric value of peripheral PN is: AA 60 g × 4 kcal/g = 240 kcal Lipid 50 g × 10 kcal/g = 500 kcal Dextrose 200 g × 3.4 kcal/g = 680 kcal Total calories = 240 + 500 + 680 = 1420 kcal/70 kg = 20 kcal/kg 35% of total calories are provided as lipid

AA = amino acid; PN = parenteral nutrition.

1. It will probably not meet nutritional needs based on macronutrient and micronutrient concentration restrictions (discussed earlier).
2. For additional calories, increase the percentage of calories administered as lipid.

I. Order of mixing (for manual compounding)
   1. Add dextrose, AAs, sterile water.
   2. Add phosphate.
   3. Add other electrolytes (except Ca) and trace minerals.
   4. Mix well to ensure that phosphate is evenly distributed and to prevent precipitation with Ca.
   5. Add Ca.
   6. Observe for precipitates or contaminants.
   7. Add lipid if 3-in-1 formulation. (Note: Do not mix dextrose and lipids directly, because the low pH of dextrose can destabilize the lipid emulsion.)
   8. Add vitamins last, as close to the time of PN administration as possible in acute care settings, or just before infusion in patients receiving home PN.

J. Factors associated with Ca^{2+} and phosphate precipitation in PN
   1. Increasing pH (more basic) increases the risk of Ca^{2+} and phosphate precipitation.
   2. Increasing Ca^{2+} or phosphate concentration increases the risk of precipitation.
      a. If Ca^{2+} concentration is 6 mEq/L or less and phosphate concentration is 30 mmol/L or less, the risk of precipitation is low.
      b. Calcium chloride is more likely to precipitate with phosphate than calcium gluconate; calcium chloride should never be used in compounding PN formulations.
   3. The final concentration of AA should be at least 2.5% or greater to prevent Ca^{2+} and phosphate precipitation.
      a. AAs form soluble complexes with Ca^{2+} and phosphate.
      b. AAs provide a buffer system to maintain a lower pH of the PN in an acceptable range to prevent Ca^{2+} or phosphate precipitation.
   4. As the temperature increases, the risk of precipitation increases.
      a. PN should be refrigerated if not administered within 24 hours of compounding.
      b. If refrigerated, PN should be administered within 24 hours of rewarming.
   5. A 1.2-micron filter (used for a 3-in-1 PN) might not prevent the embolism of a calcium phosphate precipitate, but it should be used anyway to reduce the risk.
   6. Order of mixing additives is important to prevent precipitation (see above)
   7. The PN should be agitated often during compounding to ensure adequate mixture into solution.

K. Medication additives in PN
   1. In general, medications should not be added to PN.
   2. Examples of medication incompatibilities are ceftriaxone (precipitates with Ca), phenytoin (can change the pH of PN), medications containing propylene glycol or ethanol as diluents (e.g., furosemide, diazepam, lorazepam, digoxin, phenytoin, etoposide), and iron dextran (trivalent cations destabilize the lipid emulsion in 3-in-1 PN formulations).
   3. Incompatible drugs should be administered through a separate intravenous catheter or a separate lumen of a central venous catheter, if possible.

4. If an incompatible intravenous drug is to be administered through the same intravenous catheter as the PN, the PN should be stopped, followed by a compatible flush before and after drug administration. The volume of flush should be sufficient to clear the entire catheter of PN and of drug (typically about 10 mL if flushing the port closest to the patient); for drugs requiring longer infusion times, see below for precautions to prevent rebound hypoglycemia with prolonged interruptions of PN.
5. Only regular insulin is compatible with PN.

L. PN complications
1. Catheter-related infections are caused primarily by *Staphylococcus aureus* and *Candida albicans.*
2. Catheter insertion complications (e.g., pneumothorax, incorrect placement) are possible.
3. Peripheral venous thrombophlebitis can occur with peripheral catheter placement. Risk is increased by day 4 of catheterization; therefore, site should be rotated every 3 days.
4. Fluid imbalance can occur.
5. Acid-base imbalances are usually related to the patient's underlying condition; however, excessive chloride salts in the PN can cause a metabolic acidosis, whereas excessive acetate salts in the PN can cause a metabolic alkalosis.
6. Hyperglycemia can lead to nosocomial and wound infections.
7. Gut atrophy can occur.
8. Overfeeding can cause hepatic steatosis, hypercapnia, hyperglycemia, and azotemia.
9. Essential fatty acid deficiency can occur.
    a. Symptoms include skin desquamation, hair loss, impaired wound healing, hepatomegaly, thrombocytopenia, fatty liver, and anemia.
    b. It can occur within 1–3 weeks of a lipid-free PN.
10. Refeeding syndrome can occur in acutely (can include critically ill patients) or chronically malnourished patients when EN or PN is initiated.
    a. Characterized by hypophosphatemia, hypokalemia, hypomagnesemia
    b. Can cause cardiac dysfunction, respiratory dysfunction, and death
    c. Prevention of refeeding syndrome:
        i. Identify patients at risk (e.g., anorexia, alcoholism, cancer, chronically ill, poor nutritional intake for 1–2 weeks, recent unintentional weight loss, malabsorption).
        ii. Initially, provide less than 50% of caloric requirements, and then advance over several days to desired goal.
        iii. Supplement vitamins before initiating PN as well as K^+, phosphate, and magnesium (if needed); monitor daily for at least 1 week; and replace electrolytes as needed (many patients will need aggressive electrolyte replacement during the first week of PN).
11. Aluminum toxicity
    a. More likely to occur in patients receiving long-term PN or in those with renal dysfunction (aluminum is eliminated renally)
    b. Accumulates in bone and interferes with bone Ca^{2+} uptake, causing osteopenia
    c. Neurotoxicity and microcytic anemia
    d. Contaminates many intravenous electrolytes and intravenous fluids
    e. Aluminum content documented on drug labels

12. Hepatobiliary disorders (includes steatosis, cholestasis, and gallbladder sludge or stones) can occur with long-term PN administration.
    a. Steatosis (or fatty liver) is associated with overfeeding and a transient elevation in aminotransferase concentration. Although it is usually benign, it can progress to fibrosis or cirrhosis in patients receiving long-term PN.
    b. Cholestasis usually occurs in children, but it can also occur in adults receiving long-term PN and can progress to cirrhosis and liver failure; a conjugated bilirubin concentration greater than 2 mg/dL is the primary sign.
    c. Gallbladder stasis is associated with the development of gallstones, sludge, and cholecystitis; it is more attributable to a lack of EN than to PN administration.
13. Osteoporosis and osteomalacia can occur in patients receiving long-term PN, and they are associated with higher protein doses (causes increased Ca^{2+} excretion) and chronic metabolic acidosis (because of insufficient acetate).

Patient Case

9. A 43-year-old male trauma patient (height 75 inches, weight 100 kg) was recently extubated and is receiving PN. His PN formula contains 35 kcal/kg, protein 1.2 g/kg, and dextrose infusing at 4.4 mg/kg/minute, and 25% of total calories as lipid. He has gradually developed symptoms of hypercapnia and has developed a respiratory acidosis. The medical team is considering strategies to correct this to avoid reintubation. Which change to the PN formula could best correct this situation?

    A. Change PN to EN and maintain current caloric goals.

    B. Reduce dextrose amount in PN to 3 mg/kg/minute and increase lipid to maintain current caloric goal.

    C. Change electrolytes to the acetate salt in the PN to correct the acid-base imbalance.

    D. Reduce the calories to 25 kcal/kg to prevent overfeeding.

M. Monitoring patients who are receiving PN
    1. Monitor for infection (temperature, WBC, intravenous access site).
    2. Monitor for peripheral vein thrombophlebitis or infiltration (if peripheral access); symptoms include pain, erythema, and tenderness or a palpable cord at the site of the peripheral vein; treat by removing catheter.
    3. Monitor fluid status (weight, edema, vital signs, input and output, temperature).
    4. Monitor nutritional status.
        a. Prealbumin is useful for monitoring the effects of long-term nutrition support in patients who are not critically ill (see EN Monitoring earlier) because it has a shorter half-life than albumin.
            i. Values
                (a) Normal range, 16–40 mg/dL
                (b) Moderate malnutrition, 11–16 mg/dL
                (c) Severe malnutrition, less than 11 mg/dL
            ii. Goal for malnourished patients is an increase of at least 3–5 mg/dL/week until within normal range.
        b. Serum albumin (normal 3.5–5 g/dL) is a poor predictor of nutritional status because it has a long half-life, and concentrations fluctuate during illness.
    5. Monitor for hyperglycemia and hypoglycemia.
        a. A common blood glucose goal is 140–180 mg/dL.
        b. Regular insulin (initially 0.05–0.2 units per gram of dextrose) can be added to the PN for patients using a consistent dosage.

c. For patients with hyperglycemia or fluctuating insulin dosages, insulin can be supplemented separately from the PN, although this practice varies by practitioner.
d. Abrupt discontinuation of PN is usually tolerated in nondiabetic patients, but rebound hypoglycemia can occur in other patients; avoid by gradually tapering off PN over 1–2 hours. Check blood glucose 30 minutes to 1 hour after discontinuing PN. If PN is discontinued abruptly, rebound hypoglycemia can be avoided by administering 5% or 10% dextrose (may not be necessary if PN is administered through a peripheral catheter).

6. Monitor for electrolyte and acid-base imbalances. The chloride and acetate salts can be adjusted on the basis of the acid-base status of the patient.
   a. For metabolic alkalosis, Na^+ and K^+ can be administered as the chloride salts.
   b. For metabolic acidosis, Na^+ and K^+ can be administered as the acetate salts (acetate is converted to bicarbonate).
   c. For respiratory acid-base disorders, correct the underlying cause or adjust the ventilator settings as needed.
7. Monitor triglyceride concentrations and withhold lipids in patients with a concentration greater than 400 mg/dL. When calculating lipid requirements, account for any drugs mixed in a lipid emulsion (e.g., propofol, clevidipine).
8. Monitor hepatic function.
9. Monitor for patient readiness for oral or EN support.
   a. Well-nourished, healthy patients can change immediately from PN to oral or EN.
   b. Older adult, debilitated, or malnourished patients may need a transition period in which oral or EN feedings are gradually increased, coinciding with a reduction in PN.

Patient Cases

10. A patient (weight 70 kg) receives propofol at 45 mcg/kg/minute. Propofol is available at a concentration of 10 mg/mL and is mixed in a 10% lipid emulsion. Assuming the patient is receiving this infusion rate for 24 hours, which best approximates the total calories provided by the propofol infusion in a 24-hour period?

    A. 200 kcal.

    B. 250 kcal.

    C. 300 kcal.

    D. 500 kcal.

11. A patient (weight 65 kg) is receiving PN after abdominal surgery. The PN contains about 1600 kcal, including 100 g of protein, 500 kcal as lipid, and 200 g of dextrose. The following additives are also included in a 24-hour infusion of PN: sodium chloride 50 mEq, sodium acetate 100 mEq, potassium acetate 60 mEq, sodium phosphate 30 mmol, magnesium sulfate 12 mEq, calcium gluconate 10 mEq/day, multivitamins 10 mL, and trace elements 3 mL. The patient has an NG tube in place that is suctioning 400–500 mL/day, which is being replaced with an infusion of 0.9% sodium chloride. After 48 hours of PN, the patient has the following laboratory values: Na^+ 140 mEq/L, K^+ 3.8 mEq/L, Cl^- 93 mEq/L, serum bicarbonate 35 mEq/L, pH 7.5, PCO_2 47 mm Hg, and bicarbonate 36 mEq/L. Which adjustment to the PN formula is best at this time?

    A. Increase lipids to provide 750 kcal and reduce dextrose to 130 g.

    B. Increase sodium acetate to 150 mEq/day and discontinue sodium chloride.

    C. Increase sodium chloride to 150 mEq/day and discontinue sodium acetate.

    D. Add sodium bicarbonate 50 mEq to PN.

Patient Cases (*Cont'd*)

Questions 12 and 13 pertain to the following case.

A 75-year-old woman (weight 50 kg) is receiving PN after an extensive bowel resection. She is expected to require about 1 week of PN. She is receiving the following macronutrients in her formula: 70% dextrose 300 mL, 20% lipid 150 mL, and 10% AA 750 mL.

12. If these macronutrients are infused over 24 hours, which choice most closely approximates the total calories this patient is receiving daily?
    A. 20 kcal/kg.
    B. 26 kcal/kg.
    C. 30 kcal/kg.
    D. 35 kcal/kg.

13. The patient has received the PN formula for 3 days. Her blood glucose concentrations have ranged from 220 to 280 mg/dL. She has orders for the following sliding scale of regular insulin: blood glucose 200–250 mg/dL, give 2 units; blood glucose 251–300 mg/dL, give 4 units; and blood glucose 301–350 mg/dL, give 6 units. She has been receiving 14–16 units of insulin daily through the sliding-scale orders. Her medical history is significant for hypertension, diabetes, chronic obstructive pulmonary disease, and colon cancer. Treatment was recently initiated with methylprednisolone 60 mg intravenously every 6 hours for a chronic obstructive pulmonary disease exacerbation. Today, the dose will be reduced to 40 mg intravenously every 8 hours. What is the best recommendation for better control of this patient's blood glucose?
    A. Add insulin glargine 10–20 units/day to PN.
    B. Change 70% dextrose in PN to D_5W.
    C. Increase the sliding-scale insulin to 4 units for blood glucose 200–250 mg/dL, 8 units for blood glucose 251–300 mg/dL, and 12 units for blood glucose 301–350 mg/dL.
    D. Add neutral protamine Hagedorn insulin (NPH) 5 units subcutaneously every 12 hours.

REFERENCES

Fluids and Electrolytes

1. Cohn JN, Kowey PR, Whelton PK, et al. New guidelines for potassium replacement in clinical practice. A contemporary review by the National Council on Potassium in Clinical Practice. Arch Intern Med 2000;160:2429-36.
2. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552.
3. Dickerson RN, Maish GO III, Weinberg JA, et al. Safety and efficacy of intravenous hypotonic 0.225% sodium chloride infusion for the treatment of hypernatremia in critically ill patients. Nutr Clin Pract 2013;28:400-8.
4. Kellum JA, Cerda J, Kaplan LJ, et al. Fluids for prevention and management of acute kidney injury. Int J Artif Organs 2008;31:96-110.
5. Kraft MD, Btaiche IF, Sacks GS, et al. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health Syst Pharm 2005;62:1663-82.
6. Luo JC, Leu HB, Hou MC, et al. Nonpeptic ulcer, nonvariceal gastrointestinal bleeding in hemodialysis patients. Am J Med 2013;126:264.
7. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013;2:CD000567.
8. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-34
9. Polderman KH, Schreuder WO, Strack van Schijndel RJ, et al. Hypernatremia in the intensive care unit: an indicator of quality of care? Crit Care Med 1999;27:1105-8.
10. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. N Engl J Med 2018;378:819-28.
11. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed. New York: McGraw-Hill, 2001.
12. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018;378:829-39.
13. Sterns RH. Hypernatremia in the intensive care unit: instant quality—just add water. Crit Care Med 1999;27:1041-2.
14. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013;126:S1-42.
15. Vincent JL, Weil MH. Fluid challenge revisited. Crit Care Med 2006;34:1333-7.
16. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 2013;309:678-88.

Nutrition

1. A.S.P.E.N. Board of Directors. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enter Nutr 2002;26(suppl):1SA-138SA.
2. Bankhead R, Boullata J, Brantley S, et al. A.S.P.E.N. enteral nutrition practice recommendations. J Parenter Enter Nutr 2009;33:122-67.
3. Boullata JI, Carrera AL, Harvey L, et al. A.S.P.E.N. safe practices for enteral nutrition therapy. J Parenter Enter Nutr 2017;41:15-103.
4. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 1. Am J Health Syst Pharm 2004;61:1938-49.
5. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 2. Am J Health Syst Pharm 2004;61:2050-7.
6. Canada T, Crill C, Guenter P. A.S.P.E.N. Parenteral Nutrition Handbook. Silver Spring, MD: American Society of Parenteral and Enteral Nutrition, 2009.
7. Marik PE. Maximizing efficacy from parenteral nutrition in critical care: appropriate patient populations, supplemental parenteral nutrition, glucose control, parenteral glutamine, and alternative fat sources. Curr Gastroenterol Rep 2007;9:345-53.

8. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. J Parenter Enter Nutr 2016;40:159-211.
9. Miller SJ. Commercial premixed parenteral nutrition: is it right for your institution? Nutr Clin Pract 2009;24:459-69.
10. Mirtallo J, Canada T, Johnson D, et al. Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. J Parenter Enter Nutr 2004;28:S39-70.
11. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. Am J Health Syst Pharm 2008;65:73-80.
12. Stapleton RD, Jones N, Heyland DK. Feeding critically ill patients: What is the optimal amount of energy? Crit Care Med 2007;35:S535-40.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Although this patient's blood pressure is not necessarily low, it is probably low compared with his baseline, considering his history of hypertension. In addition to his low blood pressure, his other signs and symptoms of intravascular volume depletion include an elevated BUN/SCr ratio, an elevated heart rate, and a reduced urine output. Crystalloids or colloids are appropriate fluids for resuscitation, making lactated Ringer solution (Answer C) the best option. Furosemide (Answer A) may increase his urine output, but at the cost of further depleting the intravascular volume. Albumin 25% (Answer B) should be avoided for fluid resuscitation because it causes a shift of fluid from the IS space into the intravascular space, which can potentiate his dehydration. Answer D would be appropriate for a maintenance infusion; however, D_5W/0.45% sodium chloride plus potassium chloride 20 mEq/L would not provide optimal replacement of the intravascular space, given the distribution in TBF.

2. Answer: C

This patient has no signs or symptoms of intravascular volume depletion; therefore, he does not require fluid resuscitation. Because he is not taking adequate fluids by mouth, he should be given maintenance intravenous fluid to prevent dehydration and electrolyte imbalances. This is typically accomplished by a combination of free water and 0.45% sodium chloride with K^+ (Answer C). The infusion rate is calculated as 1500 mL + (60 kg × 20 mL/kg) = 2700 mL/24 hours, or about 110 mL/hour. Parenteral nutrition (Answer A) is inappropriate because there is no evidence that the patient's GI tract is nonfunctional. Albumin 5% (Answer B) or lactated Ringer solution (Answer D) should be reserved for fluid resuscitation in patients with signs or symptoms of intravascular volume depletion.

3. Answer: B

Although this patient has symptomatic hyponatremia, she also has signs of intravascular volume depletion. This intravascular volume depletion is a potent stimulus for ADH secretion, which will potentiate hyponatremia. In patients with hyponatremia and intravascular volume depletion, it is important to restore intravascular volume first to prevent organ hypoperfusion and to inhibit ADH secretion. Fluid resuscitation should be accomplished with 0.9% sodium chloride as a fluid bolus, followed by a reevaluation of fluid status (Answer B). A slower infusion of 0.9% sodium chloride (Answer A) will not restore intravascular volume quickly. Once the intravascular volume is restored, ADH secretion will cease. This can be followed by a water diuresis, with a subsequent rise in the serum sodium concentration. Of importance, the patient should be monitored closely to prevent a rise in serum sodium greater than 10–12 mEq/L/day. If serum sodium rises too fast, 0.45% sodium chloride can be infused to slow the rate of rise of serum sodium concentration. Hypertonic saline (Answers C and D) would not be advisable unless the patient continues to have symptoms of hyponatremia after appropriate fluid resuscitation.

4. Answer: C

To prevent central pontine myelinolysis in patients with hyponatremia, it is recommended that the serum sodium concentration be raised by no more than 10–12 mEq/L in 24 hours (Answer C). Of note, the goal is not to achieve a normal serum sodium concentration in 24 hours. Rapid correction of chronic hyponatremia can cause permanent neurologic damage (Answers A and B), and because this patient is symptomatic, she should not be maintained at her current sodium concentration (Answer D).

5. Answer: D

This patient has hyponatremia and hypokalemia. In patients with hypokalemia, there is a reduction in IC K^+. To maintain cellular electroneutrality, Na^+ will shift into cells. As K^+ is replaced, Na^+ shifts out of cells, and the serum sodium concentration rises. Therefore, in this case, the hypokalemia should be corrected first, which will cause a subsequent improvement in the hyponatremia. Because this patient has no ECG changes related to the hypokalemia, oral supplementation with K^+ (Answer D) is recommended over intravenous replacement (Answer A). A dose of 60–80 mEq/day should cause an increase in the K^+ concentration by 0.6–0.8 mEq/L. Because the patient is eating a regular diet, she should no longer require intravenous fluids (Answer B). Hypertonic saline (Answer C) is incorrect because this patient has no serious symptoms of hyponatremia.

6. Answer: D

This patient has not been given enough water, and she cannot communicate (or feel) thirst. This can be prevented by administering about 1 mL of water for every calorie administered. It should also be prevented by monitoring serum sodium concentrations and adjusting water intake as needed. To correct the hypernatremia, water should be administered, preferably through the enteral feeding tube (Answer D). If this is not possible, it can be administered intravenously as D_5W (Answer B or C), but never as sterile water (Answer A). Sterile water administered intravenously can cause hemolysis and death. The patient's water deficit (in liters) can be estimated with the equation $0.4 \times LBW \times [(Na^+/140) - 1]$. Water should be replaced over several days, taking care to avoid changes in serum sodium greater than 10–12 mEq/L in 24 hours.

7. Answer: B

This patient has ECG changes consistent with hyperkalemia. Insulin (Answer B) will have the fastest onset and most predictable action of lowering serum potassium. Calcium gluconate (Answer A) should only be used with caution in this patient because it can potentiate digoxin toxicity and bradycardia. The efficacy of sodium bicarbonate (Answer C) is not well established. Albuterol (Answer D) can be efficacious when added to insulin, but it might not be effective in about 40% of patients; therefore, it is not recommended as initial therapy or as monotherapy for hyperkalemia.

8. Answer: C

This patient is receiving a calorie-dense EN formula that typically has less water than other enteral products. Therefore, although not currently hypernatremic, the patient is at risk of developing hypernatremia because of insufficient water intake. This can be prevented by administering additional water. The preferred route is enteral, if possible. The additional water needed on a daily basis can be estimated as 1 mL/kcal or around 30 mL/kg/day. Therefore, if this patient is receiving enteral feeding at 35 mL/hour × 2 kcal/mL, she is receiving 1680 kcal/day. She is receiving only 717 mL of water per liter of enteral formula, which is 602 mL/day for the 840 mL of enteral feeding daily (35 mL/hour × 24 hours = 840 mL/day). Because she is receiving 1680 kcal, she needs about 1680 mL of water per day. Subtracting the water from the feedings from the total needed, 1680 − 602 = 1078 mL is needed. This can be divided and administered through the gastric feeding tube at about 180 mL/dose every 4 hours (Answer C). Of note, the patient should be monitored for fluid overload, especially given her chronic kidney disease. Given this patient's stable kidney disease and her adequate urine output, she should be able to tolerate this amount of free water. The amount of free water needed daily is an estimation that should be adjusted on the basis of specific patient parameters (e.g., serum sodium, input, output, daily weight, edema). Free water should not be administered as intravenous dextrose (Answer B) unless enteral administration is not feasible. Answer A is incorrect because reducing Na^+ will not prevent hypernatremia; the problem is related to too little water rather than too much Na^+. Answer D is incorrect because the caloric goals should not be sacrificed, and they would not eliminate the problem of insufficient water administered.

9. Answer: D

This patient is developing a respiratory acidosis, possibly because of overfeeding. Although dextrose is metabolized to water and CO_2, it generally will not cause a respiratory acidosis unless the patient is being overfed. Reducing the total calories to 25 kcal/kg decreases the risk of overfeeding, and reintubation can be avoided (Answer D). Answer A is incorrect because patients can be overfed with PN or EN. Answer B is incorrect because, even if the dextrose in the PN is reduced, the patient can still develop symptoms of overfeeding. Answer C is incorrect because the underlying (overfeeding) cause should be corrected, rather than adjusting the acetate to treat a respiratory acidosis.

10. Answer: D

To determine the amount of calories provided by propofol, it must first be determined how many milliliters per day are infused. For this patient receiving propofol 45 mcg/kg/minute and weighing 70 kg, 454 mL is infused daily (assuming a constant infusion rate). Next, if a 10% lipid emulsion provides about 1.1 kcal/mL, it can be calculated that 454 mL/day of propofol provides about 500 kcal/day, making Answer D correct and Answers A–C incorrect.

11. Answer: C

This patient has developed a metabolic alkalosis, probably secondary to the loss of gastric fluid through NG suctioning. The low serum chloride and elevated serum bicarbonate concentrations support this theory. In addition, the acid base is consistent with metabolic alkalosis with compensatory respiratory acidosis. The treatment in this circumstance is to replace the lost fluid with 0.9% sodium chloride, which is being done. In addition, Na^+ and K^+ can be administered as the chloride salt rather than the acetate salt (Answer C). For this case, only Na^+ is converted to chloride salt, and K^+ is left as the acetate salt initially. With daily monitoring, the ratio of Cl^- to acetate can be adjusted further if needed. Answer B is incorrect because it would probably worsen the metabolic alkalosis as the sodium acetate is converted to bicarbonate. Answer A is incorrect because hypercapnia is a compensatory response, not the primary acid-base disturbance. Answer D is incorrect for several reasons. First, it is never advisable to add sodium bicarbonate to PN because of incompatibility and the risk of calcium-phosphate precipitation. Second, sodium bicarbonate is the incorrect treatment for metabolic alkalosis because it can worsen alkalosis.

12. Answer: B

The total calories are calculated by adding the calories provided by dextrose, lipid, and AA. Dextrose provides 714 kcal (210 g × 3.4 kcal/g), lipid provides about 300 kcal (30 g × 10 kcal/g), and AA provides 300 kcal (75 g × 4 kcal/g). Adding these together provides calories of 1314 kcal/50 kg = 26.3 kcal/kg, making Answer B correct and Answers A, C, and D incorrect.

13. Answer: D

This patient's hyperglycemia could be attributable to either stress or corticosteroids. Because the corticosteroid dose is being tapered, the blood glucose concentrations will probably decrease with time. For patients with a fluctuating blood glucose concentration, it can be difficult to add insulin to PN because insulin cannot be adjusted in a timely manner. Regardless, Answer A is incorrect because long-acting insulin should not be added to PN. If insulin is added to PN, it should be regular insulin. Although some experts promote "permissive underfeeding," Answer B is incorrect because it would provide insufficient calories for this patient. Sliding scales of insulin can be useful when used in conjunction with a baseline of insulin in patients with a fluctuating blood glucose concentration. However, a sliding scale (Answer C) should not be used as the primary intervention for blood glucose control, because it is reactive and it fails to prevent hyperglycemia. In addition, the sliding scale described recommends insulin only when the blood glucose reaches 200, which is too high. Answer D is correct because it provides a baseline of insulin that can be adjusted in a timely manner as the blood glucose concentrations fluctuate according to the patient's status.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient continues to have hypotension and tachycardia, both of which are signs of intravascular volume depletion. The improvement in blood pressure and tachycardia after a fluid bolus also indicates intravascular volume depletion. Fluid administration should continue until there is no further improvement in vital signs. Patients with intravascular volume depletion require a rapid bolus of crystalloid (either 0.9% sodium chloride or lactated Ringer solution) of 500–1000 mL (or about 30 mL/kg), followed by reassessment (Answer D). A rapid bolus is essential to prevent organ dysfunction caused by hypoperfusion. Although the patient has poor urine output, administering furosemide (Answer A) will worsen volume depletion. As volume is replaced, urine output will probably increase. Administering 5% albumin in combination with a vasopressor (Answer B) should not be the initial treatment as long as vital signs are improving with the administration of fluid boluses with 0.9% sodium chloride. In addition, colloids are more expensive, and there is no evidence of better outcomes for fluid resuscitation with colloids than with crystalloids. Furthermore, infusion of albumin over 4 hours is incorrect because it would not restore intravascular volume rapidly enough to prevent organ dysfunction. Intravenous fluid containing D_5W (Answer C) is not appropriate for fluid resuscitation, regardless of the blood glucose concentration.

2. Answer: A

To answer this question, an alligation must first be set up using 0.9% and 23.4% sodium chloride. If 0.9% sodium chloride contains 154 mEq/L, 2% should contain about 342 mEq/L. After completing the alligation, the correct amounts can be double-checked by verifying the amount of sodium chloride in the prepared product: 951 mL of 0.9% sodium chloride contains 146 mEq of sodium chloride, and 49 mL of 23.4% sodium chloride contains 196 mEq of sodium chloride; therefore, 146 mEq + 196 mEq = 342 mEq/L of sodium chloride in the final product. The osmolarity is calculated as (2 g/100 mL) × (1 mol/58.5 g) × (2 Osm/mol) × (1000 mOsm/Osm) × (1000 mL/L) × 0.93 = 635 mOsm/L (Answer A is correct; Answer D is incorrect). Because of the osmotic coefficient (0.93), the sodium chloride does not completely dissociate in solution. Although use of the osmotic coefficient provides a more accurate osmolarity, it is probably not clinically relevant in calculating the osmolarity of intravenous sodium chloride. Therefore, it is safe to estimate the osmolarity of sodium chloride as either 635 or 684 mOsm/L, because there is no apparent clinical difference between these osmolarities. Because the osmolarity is less than 900 mOsm/L, the infusion can be administered through a peripheral line, (Answers B and C are incorrect).

3. Answer: D

In this case, hyponatremia is likely because of congestive heart failure and has probably developed over a prolonged period (not acute onset). Patients with chronic hyponatremia because of heart failure are typically asymptomatic. Rapid correction of chronic hyponatremia is associated with permanent neurologic damage caused by central pontine myelinolysis. Furthermore, hypertonic saline can worsen volume overload in patients with heart failure. Although hyponatremia is a sign of worsening heart failure, correction of hyponatremia in patients with heart failure does not improve outcomes (Answer D). For these reasons, the risks of correcting the serum sodium with hypertonic saline (Answers A–C) outweigh the potential benefits.

4. Answer: B

Patients with hyperkalemia and ECG changes should be treated first with Ca^{2+} for cardiac stability (Answer B). After Ca^{2+} administration, other measures can be taken to shift K^+ from the EC compartment to the IC compartment. Insulin (Answer A) can accomplish this; however, in this patient with hyperglycemia, insulin should be administered without glucose. Sodium polystyrene sulfonate (Kayexalate; Answer C) can be administered, but it is not effective immediately and is therefore not appropriate for first-line treatment of symptomatic hyperkalemia. Sodium bicarbonate (Answer D) is incorrect because it does not treat cardiac instability.

5. Answer: C

This patient is not receiving adequate nutritional intake because of her mental status. Because her GI tract is functional, it should be used for feeding to prevent gut mucosal atrophy. An NG or nasoduodenal feeding tube is appropriate for enteral access for short-term nutritional support (Answer C). A percutaneous gastrostomy tube (Answer D), which requires a surgical procedure,

is used for long-term nutritional support. The patient should receive 25–35 kcal/kg/day. The PN formulas (Answers A and B) should not be used in a patient with a functional GI tract. Although Answer B would be an appropriate PN formula for peripheral administration, PN is associated with more complications than EN is.

6. Answer: C

This correct formula provides about 30 kcal/kg of calories, 1.5 g of protein per kilogram (AA), and 30% of total calories as lipid (Answer C). Answer A is incorrect because it provides 1000 calories as lipid, which is about 62% of the total calories provided. Answer B is incorrect because it contains only 0.8 g/kg of AA, which is an insufficient amount considering the patient's stress and apparent absence of kidney injury. Answer D is incorrect because it contains too much AA.

7. Answer: B

This patient has hypomagnesemia and hypokalemia. Correction of hypokalemia requires correction of hypomagnesemia to prevent renal loss of K^+ (Answer B). Magnesium should be administered slowly to avoid hypotension and increased renal excretion caused by rapid administration. Continued K^+ should not be given until magnesium is administered (Answers A and C). Calcium correction will not have a large effect on K^+ correction (Answer D).

8. Answer: C

Enteral nutrition prevents gut mucosal atrophy and subsequent bacterial translocation (Answer C). Bacterial translocation is the crossing of bacteria from the GI tract into the systemic circulation. Enteral nutrition is associated with fewer infectious complications than PN, which may partly be because of a reduction in bacterial translocation (Answers A and B). Zinc does not affect atrophy and bacterial translocation (Answer D).

9. Answer: C

It is a common misconception that all patients with kidney failure need protein restriction (Answers A and B). This is true for chronic kidney disease patients who are not undergoing dialysis. Conversely, if they are undergoing dialysis, they do not need protein restriction and can receive AA at 1.2–1.5 g/kg/day (Answer C). Answer D is incorrect because too much protein is given.

Critical Care

Corey J. Witenko, Pharm.D., BCPS, BCCCP

NewYork-Presbyterian Hospital
New York, New York

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Corey J. Witenko, Pharm.D., BCPS, BCCCP

NewYork-Presbyterian Hospital
New York, New York

Learning Objectives

1. Interpret hemodynamic parameters and acid-base status in critically ill patients.
2. Differentiate between presentation of and treatment strategies for hypovolemic, obstructive, cardiogenic, and distributive shock.
3. Discuss the appropriate use of fluids, vasopressors, antibiotics, and corticosteroids in patients with sepsis or septic shock.
4. Discuss strategies to optimize the safety and efficacy of therapeutic hypothermia for patients after cardiac arrest.
5. Recommend therapeutic options to minimize delirium and provide optimal analgesia, sedation, neuromuscular blockade, and nutritional support in critically ill patients.
6. Recommend therapeutic options to prevent stress ulcers, venous thromboembolism, hyperglycemia, and ventilator-associated pneumonia in critically ill patients.
7. Recommend treatment options for acute intracranial hemorrhage.

Abbreviations in This Chapter

ABG	Arterial blood gas
AG	Anion gap
AHA	American Heart Association
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
BPS	Behavioral Pain Scale
BUN	Blood urea nitrogen
CAM-ICU	Confusion Assessment Method for the ICU
CI	Cardiac index
CPOT	Critical-Care Pain Observation Tool
CPR	Cardiopulmonary resuscitation
CVP	Central venous pressure
D_5W	5% Dextrose
DBP	Diastolic blood pressure
EN	Enteral nutrition
EPS	Extrapyramidal symptoms
Fio_2	Fraction of inspired oxygen
GI	Gastrointestinal
H_2	Histamine-2
HIT	Heparin-induced thrombocytopenia
ICDSC	Intensive Care Delirium Screening Checklist
ICH	Intracranial hemorrhage
ICU	Intensive care unit
INR	International normalized ratio
IPH	Intraparenchymal hemorrhage
LMWH	Low-molecular-weight heparin
MAP	Mean arterial pressure
OGT	Orogastric feeding tube
$PaCO_2$	Partial pressure of carbon dioxide
PAOP	Pulmonary artery occlusion pressure
PCWP	Pulmonary capillary wedge pressure
PN	Parenteral nutrition
PPI	Proton pump inhibitor
PPV	Pulse pressure variation
RASS	Richmond Agitation-Sedation Scale
RQ	Respiratory quotient
SAH	Subarachnoid hemorrhage
SAS	Sedation-Agitation Scale
SBP	Systolic blood pressure
SSC	Surviving Sepsis Campaign
SUP	Stress ulcer prophylaxis
SVR	Systemic vascular resistance
SVV	Stroke volume variation
TOF	Train-of-four
VTE	Venous thromboembolism
WBC	White blood cell count

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 58-year-old woman remains intubated in the intensive care unit (ICU) after a recent abdominal operation. In the operating room, she receives more than 10 L of fluid and blood products, but has received aggressive diuresis with furosemide postoperatively. In the past 3 days, she has generated 12 L of urine output, and her blood urea nitrogen (BUN) and serum creatinine (SCr) have steadily increased to 40 and 1.5 mg/dL, respectively. Her urine chloride (Cl) concentration was 9 mEq/L (24 hours after her last dose of furosemide). This morning, her arterial blood gas (ABG) reveals pH 7.50, $Paco_2$ 46 mm Hg, and bicarbonate (HCO_3^-) 34 mEq/L. Her vital signs include blood pressure 85/40 mm Hg and heart rate 110 beats/minute. Which action is best to improve her acid-base status?

A. 0.9% sodium chloride bolus.
B. 5% dextrose (D_5W) bolus.
C. Hydrochloric acid infusion.
D. Acetazolamide intravenously.

2. A 21-year-old man (weight 80 kg) admitted 1 day ago after a gunshot wound to the abdomen is receiving mechanical ventilation and is thrashing around in bed and pulling at his endotracheal tube. His score is +3 on the Richmond Agitation-Sedation Scale (RASS). The patient is negative for delirium according to the Confusion Assessment Method for the ICU (CAM-ICU). His pulmonary status precludes extubation, and the attending physician estimates that he will remain intubated for at least 48 more hours. The medical team has decided that his RASS goal should be between 0 and -1. He is receiving a fentanyl infusion (150 mcg/hour), which has been adequately controlling his pain (Critical-Care Pain Observation Tool [CPOT] less than 3 for 24 hours). Vital signs include blood pressure 110/70 mm Hg and heart rate 110 beats/minute. His baseline QTc interval is 460 milliseconds. Which is the best intervention for achieving this patient's RASS goal?
   A. Initiate a dexmedetomidine 1-mcg/kg loading dose over 10 minutes, followed by 0.2 mcg/kg/hour.
   B. Initiate a lorazepam 3-mg intravenous load, followed by a lorazepam 3-mg/hour infusion.
   C. Initiate propofol at 5 mcg/kg/minute and titrate by 5 mcg/kg/minute every 5 minutes as needed.
   D. Initiate haloperidol 1 mg intravenously, and double the dose every 20 minutes as needed.

3. A 62-year-old woman is admitted to the medical ICU for respiratory dysfunction necessitating mechanical ventilation. She has no significant medical history. Her chest radiograph reveals bilateral lower lobe infiltrates, her white blood cell count (WBC) is 21×10^3 cells/mm^3, lactate is 1.7 mmol/L, temperature is 103.3°F (39.6°C), blood pressure is 82/45 mm Hg (normal for her is 115/70 mm Hg), heart rate is 110 beats/minute, and respiratory rate is 22 breaths/minute. After she is given a diagnosis of community-acquired pneumonia, she is empirically initiated on ceftriaxone 2 g/day and azithromycin 500 mg/day intravenously. After fluid resuscitation with 6 L of lactated Ringer solution, her blood pressure is unchanged. Dopamine is initiated and titrated to 9 mcg/kg/minute, with a resulting blood pressure of 96/58 mm Hg, and her heart rate is 138 beats/minute. She has made less than 100 mL of urine during the past 6 hours, and her SCr has increased from 0.9 mg/dL to 1.3 mg/dL. Her serum albumin concentration is 2.7 g/dL. Which therapy is best for this patient at this time?
   A. Administer 5% albumin 500 mL intravenously over 1 hour and reassess mean arterial pressure (MAP).
   B. Initiate hydrocortisone 50 mg intravenously every 6 hours.
   C. Change dopamine to norepinephrine 0.01 mcg/kg/minute to maintain a MAP greater than 65 mm Hg.
   D. Reduce the dopamine infusion to 1 mcg/kg/minute to maintain a urine output of at least 1 mL/kg/hour.

4. A 92-year-old woman is admitted to the ICU with urosepsis and septic shock. She lives in a long-term care facility and has a medical history significant for coronary artery disease and hypertension. Her blood pressure is 72/44 mm Hg, central venous pressure (CVP) is 5 mm Hg, heart rate 120 beats/minute, and oxygen saturation (Sao_2) is 99%; her laboratory values are normal, except for a BUN of 74 mg/dL and Cr of 2.7 mg/dL (baseline of 1.5 mg/dL). Her urine output is about 20 mL/hour. Appropriate empiric antibiotics were initiated. Which therapy is most appropriate to initiate next?
   A. Norepinephrine 0.05 mcg/kg/minute.
   B. Lactated Ringer solution 500-mL bolus.
   C. Dopamine 5 mcg/kg/minute.
   D. Albumin 5% 500-mL bolus.

5. A 46-year-old man had a witnessed cardiac arrest in an airport terminal. After about 5 minutes, emergency medical services arrived, and defibrillator pads were applied. The cardiac monitor showed ventricular tachycardia (VT), and the patient had no discernible pulse. He was defibrillated with 200 J without return of spontaneous circulation

(ROSC). He received an additional two shocks of 200 J with no improvement. Between shocks, the patient received cardiopulmonary resuscitation (CPR). An intravenous line was obtained, and an epinephrine 1-mg intravenous push was given; chest compressions and artificial respirations were initiated. Within 1 minute, the patient was reassessed. The cardiac monitor still showed VT, and he remained pulseless; therefore, another shock of 200 J, followed by an amiodarone 300-mg intravenous push, was administered. After this, the patient was converted to a normal sinus rhythm with a heart rate of 100 beats/minute. The patient was then transported to the hospital, intubated and unresponsive. Which recommendation is most likely to improve this patient's outcomes?

A. Administer sodium bicarbonate intravenously.
B. Administer vasopressin 40 units intravenously.
C. Administer a continuous infusion of heparin.
D. Initiate a targeted temperature management protocol.

6. A 72-year-old man is admitted to the medical ICU for post-cardiac arrest care with therapeutic hypothermia. His body temperature was maintained at 91.4°F (33°C) for 24 hours, and the health care team decides it is time to rewarm slowly at 0.5°C every hour. Which is most important to consider during the rewarming phase?

A. Frequent laboratory monitoring is necessary to guide potassium supplementation because of the risk of hypokalemia.
B. A vecuronium continuous infusion should be administered to prevent shivering.
C. Phenytoin should be administered for seizure prophylaxis.
D. Frequent blood glucose monitoring is necessary, given the risk of hypoglycemia.

7. A 65-year-old man with a history of hypothyroidism, heart failure, and myocardial infarction is admitted to the ICU with severe community-acquired pneumonia. Six hours after admission, he develops acute respiratory failure, hypotension, and acute kidney injury from presumed sepsis. He is placed on mechanical ventilation, and a nasogastric tube is placed, with no plans for extubation. Which is most appropriate for this patient's stress ulcer prophylaxis (SUP)?

A. Administer sucralfate 1 g four times daily by nasogastric tube.
B. Administer magnesium hydroxide 30 mL four times daily by nasogastric tube.
C. Administer famotidine 20 mg intravenously daily.
D. No prophylaxis is indicated for this patient because he has no risk factors for SUP.

8. A 45-year-old man is admitted to the ICU with H1N1 causing respiratory failure. He is intubated and sedated with fentanyl 200 mcg/hour and propofol 25 mcg/kg/minute. He has received 4 L of lactated Ringer solution and 1 L of albumin and is currently receiving norepinephrine 0.15 mcg/kg/minute and vasopressin 0.03 unit/minute for hemodynamic support. His current vital signs are blood pressure 85/58 mm Hg, heart rate 99 beats/minute, and respiratory rate 18 breaths/minute. Which is the best plan for this patient's steroid therapy?

A. Initiate hydrocortisone 50 mg every 6 hours intravenously.
B. Perform a cosyntropin stimulation test and initiate hydrocortisone 50 mg every 6 hours intravenously if the patient does not have an increase greater than 9 mcg/dL from baseline.
C. Check a random cortisol and initiate hydrocortisone 50 mg every 6 hours intravenously if the result is less than 10 mcg/dL.
D. Steroids are not indicated at this time.

9. A 19-year-old man (height 71 inches [180 cm], weight 68 kg) is admitted to the ICU after ingesting an unknown quantity of acetaminophen. After initial resuscitation and treatment with acetylcysteine, the patient remains unresponsive and intubated. The intensivist would like to start enteral nutrition (EN) as soon as possible. Which is the best way to calculate the patient's caloric and protein needs?

A. Estimate caloric needs at 25 kcal/kg and protein at 1.2 g/kg.
B. Perform indirect calorimetry to estimate caloric and protein needs.

C. Estimate caloric needs at 14 kcal/kg and protein at 2 g/kg.

D. Calculate caloric needs based on the Mifflin equation, and order a prealbumin concentration to assess protein needs.

10. A 57-year-old woman is admitted to the ICU with injuries sustained after a fall from 12 feet. She has traumatic brain injury and has been intubated for airway protection. What is the best intervention to prevent ventilator-associated pneumonia in this patient?

A. Initiate pantoprazole 40 mg intravenously daily.

B. Perform selective digestive decontamination with enteral polymyxin B sulfate, neomycin sulfate, and vancomycin hydrochloride.

C. Maintain head of bed elevation at 20 degrees at all times.

D. Start chlorhexidine 0.12% oral swabs twice daily.

11. You are the critical care pharmacist for a 300-bed hospital. The critical care committee wants to institute an evidence-based glucose control protocol for the ICU. What is the best goal to implement for patients who present with septic shock?

A. Check blood glucose every 6 hours and treat with sliding scale protocol when greater than 180 mg/dL.

B. Initiate insulin infusion with a target of 110–140 mg/dL for two blood glucose values greater than 140 mg/dL.

C. Initiate insulin infusion with a target of 110–180 mg/dL for two blood glucose values greater than 180 mg/dL.

D. Initiate insulin infusion with a target blood glucose of 80–110 mg/dL for two blood glucose values greater than 150 mg/dL.

12. Which is the most appropriate therapy to reduce the risk of delayed ischemia and improve neurologic outcomes after an aneurysmal subarachnoid hemorrhage (SAH)?

A. Clevidipine continuous infusion titrated to maintain an SBP less than 160 mm Hg.

B. Nimodipine 60 mg every 4 hours for 21 days.

C. Norepinephrine continuous infusion titrated to maintain an SBP greater than 160 mm Hg.

D. Amlodipine 10 mg every 24 hours for 21 days.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Tasks 1, 2, 3
2. Domain 2: Application of Evidence to Practice and Education
    a. Task 2

I. INTERPRETATION OF HEMODYNAMIC PARAMETERS

A. Hemodynamics (Table 1)
   1. Arterial blood pressure is the product of cardiac output and resistance to flow (systemic vascular resistance [SVR]).
      a. Cardiac output (milliliters of blood pumped per minute) consists of stroke volume (milliliters of blood ejected from the left ventricle per beat) and heart rate.
      b. Stroke volume is determined by preload (amount of blood available to eject), afterload (resistance to ejection), and contractility (amount of force generated by the heart). These will be discussed in more detail later.
   2. Arterial blood pressure can be described by systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean arterial pressure (MAP). This is the driving pressure for organ perfusion and oxygen delivery. MAP = [SBP + (2 × DBP)]/3. Note that MAP is based largely on DBP because most of the cardiac cycle is spent in diastole.
      a. Normal MAP is 70–100 mm Hg.
      b. MAP is an indication of global perfusion pressure; a MAP of at least 65 mm Hg is necessary for adequate cerebral perfusion in most patients.
      c. MAP can be calculated using the above equation, but direct measurement from an arterial line provides more timely and accurate measurements.
   3. Preload is defined as ventricular end-diastolic volume, and it increases proportionally with stroke volume (Frank-Starling mechanism). Commonly used measures of preload include CVP, PCWP, or pulmonary artery occlusion pressure (PAOP), and newer measures such as stroke volume variation (SVV) and pulse pressure variation (PPV).
      a. CVP is the pressure in the vena cava at the point of blood returning to the right atrium and may reflect volume status, although its utility in assessing volume responsiveness (i.e., whether a patient's low blood pressure will improve with an increase in intravascular volume) is poor. A CVP of 8–12 mm Hg (12–16 mm Hg if mechanically ventilated because of increases in thoracic pressure) has been suggested as being optimal for a patient with hypoperfusion from sepsis, but data on the use of CVP are lacking. CVP values at the extremes usually reflect hypovolemia (less than 2 mm Hg) and hypervolemia (greater than 18 mm Hg).
      b. PCWP or PAOP is the pressure when a balloon is inflated (wedged) in one of the pulmonary artery branches. Because the measurement is taken closer to the left ventricle than CVP, it may be a more accurate marker of volume status, but controversy remains. Its utility is diminished because the use of pulmonary artery catheters has severely declined.
      c. Dynamic markers (SVV, PPV) are increasingly used to determine a patient's volume responsiveness to a fluid challenge. These measurements consider other variables and provide a better assessment of an individual patient's position on the Starling curve. Further information about dynamic markers can be found in the references. (Curr Opin Crit Care 2013;19:234-41)

B. Indicators of oxygen delivery
   1. Assessment of end organ function is perhaps the simplest measurement of adequate oxygen delivery. Changes in mental status, decreased urine output (less than 0.5 mL/kg/hour), and cold extremities may be the first markers of organ hypoperfusion.
   2. Blood pressure is the driving force behind oxygen delivery. Every organ is able to autoregulate blood flow, but this ability is generally lost at MAP values less than 65 mm Hg.
   3. Lactic acid
      a. Lactic acid is formed during anaerobic metabolism.
      b. During states of hypoperfusion, the tissues receive less blood and therefore less oxygen.

c. If there is less oxygen for the tissues, they will use anaerobic metabolism, with the subsequent production of lactic acid.
d. Lactate clearance can be used as a therapeutic end point in shock states.

4. Venous oxygen saturation
   a. The oxyhemoglobin saturation of venous blood returning to the right atrium is normally 70%–75% (with a normal [99%–100%] arterial oxygen saturation), indicating that the normal oxygen extraction ratio is around 25%–30%.
   b. In times of decreased oxygen delivery (caused by anemia, a decrease in Sa_{O_2}, CO, or tissue perfusion), more oxygen is extracted from the blood that is being perfused to tissues, causing an increased extraction ratio and thus a decrease in venous oxygen saturation.
   c. Central venous oxygen saturation (Scv_{O_2}) and mixed venous oxygen saturation (Sv_{O_2}) are measurements of venous oxygen saturation. These values are similar, but Scv_{O_2} is slightly higher than Sv_{O_2} because it has not mixed with venous blood from the coronary sinus. Scv_{O_2} is measured in the superior vena cava, and Sv_{O_2} is measured from the pulmonary artery; therefore, Sv_{O_2} is about 5% lower than Scv_{O_2}.
   d. A normal Sv_{O_2} does not rule out hypoperfusion in patients with impaired extraction (e.g., sepsis). An elevated lactate concentration may indicate hypoperfusion in this scenario.

Table 1. Hemodynamic Parameters and Normal Values

Parameter	Calculation (If Applicable)	Normal Range
Systolic blood pressure (SBP)		90–140 mm Hg
Diastolic blood pressure (DBP)		60–90 mm Hg
Mean arterial blood pressure (MAP)	[SBP + (2 × DBP)]/3	70–100 mm Hg
Systemic vascular resistance (SVR)	80 [(MAP – CVP)/CO]	800–1200 dynes/s/cm^5
Heart rate (HR)		60–80 beats/min
Cardiac output (CO)	HR × SV	4–7 L/min
Cardiac index (CI)	CO/BSA	2.5–4.2 L/min/m^2
Stroke volume (SV)	CO/HR	60–130 mL/beat
Pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusion pressure (PAOP)		5–12 mm Hg
Central venous pressure (CVP)		2–6 mm Hg
Lactic acid		<1 mmol/L
Central venous oxygen saturation (Scv_{O_2})		70%–75%

BSA = body surface area.

II. TREATMENT OF SHOCK

A. Diagnosis of shock is based on hemodynamic parameters. Many patients have more than one type of shock (Table 2).

Table 2. Definitions of Shock

Hemodynamic Subset	CI	CVP/PCWP	SVR	Description
Hypovolemic	Low	Low	High	To understand why patients with hypovolemia have a low CI, the Starling curve illustrates reduced cardiac function as intravascular volume is reduced The reduced intravascular volume is indicated by a low PCWP, with a reflex increase in SVR to maintain tissue perfusion SVR is inversely related to flow (CI)
Cardiogenic	Low	High	High	Patients with cardiogenic shock have acute heart failure (low CI) The insufficient forward flow of blood causes venous congestion (high PCWP) and an underfilled arterial blood volume The subsequent reduced tissue perfusion causes a reflex vasoconstriction (which, although it can improve blood flow to vital organs, can worsen heart function by increasing afterload) and reduced renal excretion of Na^+ and water
Obstructive	Low	Low (impaired ejection) High (impaired filling)	High	Impairment in diastolic filling (caused by tamponade) or systolic contraction (massive pulmonary embolus, aortic stenosis) Differentiation can usually be made by patient history
Distributive or vasodilatory	High (early) Low (late)	Low (early) Normal to high (late)	Low (early and late)	Patients with distributive shock are typically hyperdynamic (high CI), with vasodilation (low SVR) and increased vascular permeability ("leaky capillaries"), causing intravascular fluid to shift into the interstitial spaces (thus, low PCWP) The vasodilation and vascular permeability are attributable to cytokines and inflammatory mediators

CI = cardiac index; CVP = central venous pressure; Na^+ = sodium; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

B. Treatment of hypovolemic shock
   1. Treatment focuses on restoring intravascular volume and oxygen-carrying capacity. Crystalloids and colloids are discussed in the "Fluids, Electrolytes, and Nutrition" chapter.
   2. Blood products (packed red blood cells and coagulation factors) should be administered in hypovolemic shock, if clinically indicated.
      a. A hemoglobin less than 7 g/dL is defined as a transfusion threshold in patients in the general ICU. It is reasonable to have higher hemoglobin targets in selected patients (e.g., patients with symptomatic cardiovascular disease may need a hemoglobin greater than 10 g/dL).
      b. Actively bleeding patients should have blood products administered regardless of hemoglobin concentration in conjunction with interventions to stop the source of bleeding.
   3. Patients may need vasopressors if hypotension is not rapidly reversed with fluid resuscitation.
      a. The efficacy of vasopressors is reduced in patients who have not received adequate intravascular volume resuscitation.
      b. Adverse events associated with vasopressors (e.g., arrhythmias, ischemia) are greater in patients who have not received adequate fluid resuscitation.

C. Treatment of cardiogenic shock
   1. Cardiogenic shock involves injury to the left or right ventricle, resulting in reduced cardiac output and perfusion. Causes of myocardial injury are extensive and can be ischemic (e.g., myocardial infarction) and non-ischemic (e.g., myocarditis, valvular disease, medication nonadherence). Injury can be multifactorial and be present with other types of shock.
   2. Management depends on the underlying chronic or acute cardiovascular diseases, and treatment considerations vary depending on the hemodynamic indices. Details are discussed in the "Acute Care in Cardiology" chapter.

D. Treatment of obstructive shock
   1. Fluids and vasopressors can be used temporarily to improve end organ perfusion, but may not improve outcomes.
   2. Treatment of the actual obstruction is the only way to reverse the shock state.
      a. Massive pulmonary embolism: Thrombectomy or administration of systemic or catheter-directed thrombolytics may be indicated if the patient has a high risk of death.
      b. Cardiac tamponade: Removal of fluid in the pericardial sac is the only definitive treatment.

E. Treatment of vasodilatory and distributive shock
   1. Septic shock is the most common cause of vasodilatory shock (Table 3). Other causes such as anaphylaxis, vasoplegia, intoxication, pancreatitis, and neurogenic and endocrine causes will not be discussed in this section.

Table 3. Classification of Sepsis Syndromes

	Definition	Criteria
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection	Outside the ICU Infection *plus* Two or more qSOFA points 1. Altered mental status (GCS score < 15) 2. Increased respiratory rate (≥ 22 breaths/min) 3. SBP ≤ 100 mm Hg
		Inside the ICU Infection *plus* An acute change in total SOFA score ≥ 2 points consequent to the infection[a]
Septic shock	Septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone	Need for vasopressors to maintain MAP ≥ 65 mm Hg *and* Lactate > 2 mmol/L despite adequate fluid resuscitation

[a]Baseline SOFA score can be assumed to be zero in patients without preexisting organ dysfunction.

GCS = Glasgow Coma Scale; ICU = intensive care unit; MAP = mean arterial pressure; qSOFA = quick Sequential Organ Failure Assessment; SBP = systolic blood pressure; SOFA = Sequential Organ Failure Assessment.

2. The hallmark treatments of septic shock are rapid antibiotic administration and fluid resuscitation, ideally within the first hour of hypotension.
3. The Surviving Sepsis Campaign (SSC) is an initiative to reduce mortality from sepsis and septic shock.
4. SSC hour-1 bundle
    a. The SSC bundle is a group of selected elements of care taken from evidence-based practice guidelines that, when implemented as a group, have a greater effect on outcomes than any individual element. In 2016, after publication of three trials on early goal-directed therapy, the sepsis guidelines were updated.
    b. The SSC recommends the following bundle to be completed within 1 hour for patients presenting with sepsis or septic shock.
        i. Measure baseline lactate concentration.
            (a) Guide resuscitation to normalize lactate in patients with elevated lactate concentrations as a marker of tissue hypoperfusion.
        ii. Obtain blood cultures before administering antibiotics.
        iii. Administer appropriate broad-spectrum antibiotics depending on the suspected source of infection and likely pathogens.
        iv. Begin administering 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L or greater.
            (a) Albumin can be considered when patients need a substantial amount of crystalloids. There is no evidence that colloids are superior to crystalloids in improving outcomes, and they are more expensive.
            (b) Hydroxyethyl starches (e.g., hetastarch) are not recommended for fluid resuscitation because of an increased risk of acute kidney injury and mortality.
            (c) Administration of large volumes of chloride-rich solutions leads to metabolic acidosis and acute kidney injury. The use of "balanced crystalloids" (solutions with electrolyte concentrations similar to those of extracellular fluid, such as lactated Ringer solution and Plasmalyte) for volume replacement can lead to less acute kidney injury than the use of other fluids (0.9% sodium chloride). This is probably a dose-dependent phenomenon. A recent systematic

review and meta-analysis found balanced crystalloids were associated with a lower 28- or 30-day mortality than saline in critically ill patients. Specifically, patients with sepsis had similar mortality rates but lower odds of major adverse kidney events within 30 days. Increasing evidence suggests that balanced crystalloids are preferred to saline for fluid resuscitation in critically ill patients (Ann Pharmacother 2020;54:5-13).

v. Initiate vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP 65 mm Hg or greater (Table 4).
   (a) The goal MAP of 65 mm Hg may be modified depending on patient-specific factors. A higher goal may be appropriate in patients with atherosclerosis or a history of hypertension. The individualized target MAP should correlate with improvement in other clinical parameters (e.g., lactate concentration, mental status, urine output, capillary refill).
   (b) Ideally, vasopressors should be used after restoration of intravascular volume, but in patients with septic shock and hypoperfusion, vasopressors may be necessary during fluid resuscitation to optimize perfusion of vital organs. Once intravascular volume is optimized with fluid resuscitation, vasopressors should be weaned if possible.
   (c) Vasopressors improve tissue perfusion by increasing blood pressure and/or CO. Few studies have evaluated an improvement in clinical outcomes, but differences in safety profile have been observed. Therefore, drug selection is based largely on expert opinion, practitioner experience, and patient response.
   (d) Norepinephrine is the initial vasopressor of choice. The SOAP II trial is a multicenter randomized trial of patients requiring vasopressors because of any type of shock. Enrolled patients received either blinded norepinephrine or dopamine. There was no difference in 28-day mortality, but patients receiving dopamine more commonly developed an arrhythmia, required open-label norepinephrine, and required more days with vasopressor support. The study results suggest although norepinephrine does not improve mortality compared with dopamine, it is safer and more effective.
   (e) Epinephrine can be added to or substituted for norepinephrine if needed.
   (f) Vasopressin (0.03 unit/minute) can be added to norepinephrine if needed. The efficacy of vasopressin when added to norepinephrine is similar to that of norepinephrine alone. Vasopressin can have a vasopressor-sparing effect, although mortality is not improved with the combination. The addition of vasopressin earlier (at norepinephrine doses of less than 15 mcg/minute) may be associated with an improvement in outcomes.
   (g) Dopamine is an alternative to norepinephrine, but it is associated with a higher incidence of tachyarrhythmias compared with norepinephrine. Dopamine use should be limited to patients with a low risk of tachyarrhythmias and absolute or relative bradycardia. Low-dose dopamine should not be used for renal protection because evidence does not support this practice.
   (h) Phenylephrine is an alternative to consider in patients with vasopressor-induced tachyarrhythmias or persistent hypotension refractory to other vasopressors.
   (i) Use of an arterial catheter for blood pressure measurements is preferred in patients needing vasopressors, because it is a more accurate measurement of arterial pressure (compared with a blood pressure cuff) and allows continuous monitoring.
   (j) Vasopressors should be administered through a central line as soon as possible to reduce the risk of extravasation and subsequent tissue ischemia. If extravasation occurs, stop the vasopressor immediately and switch to another site if necessary. Phentolamine (an α-receptor antagonist) can be injected around the site as soon as possible to reduce tissue necrosis. In a phentolamine shortage, other options include nitroglycerin ointment (applied around the site of extravasation every 6 hours) or subcutaneous terbutaline (peripheral vasodilation is mediated through β_2-receptors).

(k) Angiotensin II is a novel vasoactive agent approved in December 2017 to increase blood pressure in adults with septic or other distributive shock. It is a peptide hormone of the renin-angiotensin-aldosterone system, causing vasoconstriction and increasing aldosterone release, which increases blood pressure. It may be used in conjunction with vasopressors, but additional studies are needed to confirm the exact role and benefit in septic shock.

vi. If persistent arterial hypotension occurs despite volume resuscitation or initial lactate 4 mmol/L or more, volume status and tissue perfusion should be reassessed by either of the following:
   (a) Repeated focused examination including vital signs, cardiopulmonary examination, capillary refill, pulse, and skin findings.
   (b) Two of the following:
      (1) CVP measurement
      (2) $Scvo_2$ measurement
      (3) Bedside cardiovascular ultrasound
      (4) Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Table 4. Vasopressors and Inotropes

Drug	Dose	α_1	β_1	β_2	DA	Notes
Norepinephrine	0.01–3 mcg/kg/min	++++	++	0	0	↓ Renal perfusion ↑ SVR, ↑ MAP ↔ to ↑ CO (at high doses) Peripheral ischemia Can induce tachyarrhythmias and myocardial ischemia
Epinephrine	0.04–1 mcg/kg/min	+++	++	++	0	Positive inotropic and chronotropic effects can induce tachyarrhythmias and myocardial ischemia Low doses primarily β-adrenergic; escalating doses primarily α-adrenergic Some evidence of reduced splanchnic circulation, which can lead to gut ischemia Increases blood glucose and lactate concentrations (type B lactic acidosis)[a] May be used for refractory hypotension
Vasopressin	0.03–0.04 unit/min	0	0	0	0	Direct stimulation of smooth muscle V1 vasopressin receptors; peripheral vasoconstriction, no adrenergic activity Theoretically beneficial because of an apparent relative vasopressin deficiency in septic shock, but no evidence of efficacy over other vasopressors (see text) Effective during acidosis and hypoxia because it does not rely on adrenergic receptors Doses ≥ 0.04 unit/min are associated with coronary vasoconstriction and peripheral necrosis Not titrated like traditional vasopressors Prone to dosing errors because of "unit/min"
Phenylephrine	0.5–8 mcg/kg/min	++++	0	0	0	↓ Renal perfusion ↑ SVR, ↑ MAP Pure α-adrenergic agonist with minimal cardiac activity Rapid ↑ SBP and DBP can cause a reflex bradycardia and reduction in CO Can be administered as a rapid bolus for acute hypotension (e.g., intraoperative) or as a continuous infusion.

Table 4. Vasopressors and Inotropes *(Cont'd)*

Drug	Dose	α_1	β_1	β_2	DA	Notes
Angiotensin II	Initial (during first 3 hr of treatment): 10–80 ng/kg/min Maintenance: 1.25–40 ng/kg/min	0	0	0	0	Binds to the G protein-coupled angiotensin receptor type 1 on vascular smooth muscle cells resulting in smooth muscle contraction, and vasoconstriction Increased risk of thrombotic events (mechanical and pharmacologic thromboprophylaxis is recommended) May cause increased heart rate, lactic acidosis, infections (e.g., fungal), and delirium Recent exposure to angiotensin-converting enzyme (ACE) inhibitors may cause an exaggerated response to angiotensin II Recent exposure to angiotensin II receptor blockers (ARBs) may cause a reduced response to angiotensin II
Dopamine	1–3 mcg/kg/min	+/–	+	+/–	++++	Lower doses cause renal, coronary, mesenteric, and cerebral arterial vasodilation and a natriuretic response Do not use low-dose dopamine for renal protection because evidence does not support this practice Lower inotropic doses can complement the vasoconstrictive effects of norepinephrine Moderate doses can ↑ contractility and SVR Effects on renal blood flow may be lost at higher doses because of predominant α1-vasoconstrictive effects Any dose can induce arrhythmias Any dose can cause endocrine changes (e.g., decreased prolactin, growth hormone, thyroid hormone); however, the clinical significance is unknown Immediate precursor of norepinephrine Prolonged infusions can deplete endogenous norepinephrine stores, resulting in a loss of vasopressor response
	3–10 mcg/kg/min	+	++	0	++	
	10–20 mcg/kg/min	+++	++	0	+	
Dobutamine	2–20 mcg/kg/min	+	+++	+	0	Positive inotrope to ↑ CO Can cause hypotension because of β_2-stimulation Higher doses can cause tachyarrhythmias and changes in BP, which can lead to myocardial ischemia
Milrinone	50-mcg/kg load over 10 min, followed by 0.375–0.75 mcg/kg/min	0	0	0	0	Noncatecholamine, phosphodiesterase inhibitor Positive inotrope Vasodilation leading to hypotension, arrhythmias possible Excreted as mostly unchanged drug in urine; renal dose adjustments necessary Loading doses often omitted especially because of increased risk of vasodilation

[a]As opposed to type A lactic acidosis caused by tissue hypoperfusion, epinephrine may cause increased lactate concentrations because of accelerated aerobic glycolysis through β-adrenergic stimulation.

BP = blood pressure; CO = cardiac output; DA = dopamine; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SVR = systemic vascular resistance.

0 = no effect

+/– = may have some effect

+ = mild effect

++ = moderate effect

+++ = strong effect

++++ = strongest effect

↓ = decreases; ↑ = increases; ↔ = no change

5. Appropriate use of antimicrobials in patients with sepsis
    a. Empiric antimicrobials should cover likely pathogens according to suspected location of infection and risk of multidrug-resistant pathogens. Common sources of infection are lung, abdomen, blood, and urinary tract. Please refer to the "Infectious Diseases" chapter for discussion of specific agents.
    b. Consider empiric fungal therapy with either triazoles such as fluconazole, an echinocandin, or a lipid formulation of amphotericin B if patients have several risk factors, including recent abdominal surgery, long-term PN, indwelling central venous catheters, or recent treatment with broad-spectrum antibiotics or if patients are immunocompromised (e.g., chronic corticosteroids or other immunosuppressants, neutropenia, malignancy, organ transplant). An echinocandin is preferred in patients with septic shock, recently treated with antifungal agents, or if *Candida glabrata* or *Candida krusei* infection is suspected.
    c. Other considerations when choosing appropriate antimicrobials include the patient's history of drug allergy or intolerance, recent antibiotic use, comorbidities, and antimicrobial susceptibility patterns in the community and hospital.
    d. Consider empiric antiviral therapy with oseltamivir for patients presenting with flulike symptoms during flu season.
    e. Begin intravenous antimicrobials as early as possible, at least within the first hour but preferably after at least two sets of blood cultures (one obtained percutaneously) are obtained. Quantitative cultures of other potential sites of infection (e.g., urine, sputum) should also be obtained before antimicrobials are administered, if possible.
    f. If several antibiotics are prescribed, administer the broadest coverage first and infuse as quickly as possible.
    g. Mortality increases by 7.6% for each 1-hour delay in administering appropriate antimicrobials.
    h. Appropriate antimicrobials do not reduce the importance of emergency source control by drainage, debridement, or device removal as needed.
    i. De-escalation should occur with respect to culture data or clinical judgment. Empiric use of combination therapy should not be administered for longer than 3–5 days if de-escalation to a single agent is appropriate.
    j. Consider discontinuing antimicrobials after 7-10 days for most serious infections. A longer course may be necessary if the patient has slow response, an undrainable foci, immunologic deficiencies, bacteremia with *S. aureus*, or some fungal or viral infections.
    k. Procalcitonin, a serum biomarker for bacterial infections, can be used as a guide for antibiotic therapy. Protocols that encourage or discourage the use of antibiotics depending on procalcitonin concentrations decrease unnecessary antibiotic use without increasing harm to patients.
    l. Discontinue antimicrobials if no infectious cause is found.

6. Indication for and use of corticosteroids
    a. Adrenal function in critically ill patients can be suppressed by endotoxins produced by bacteria and by the body's immune response to stress.
    b. Early studies showed a relationship between vasopressor responsiveness and glucocorticoid administration.
    c. To determine a patient's adrenal function during critical illness, a corticotropin stimulation test ("stim test") may be performed, although it is no longer recommended.
        i. The corticotropin stimulation test has come under criticism because of the high dose of cosyntropin administered, the inability to measure free (active) cortisol, and lack of data on outcomes of responders versus nonresponders. It is not indicated for use in the general ICU population.

d. Clinical trials of steroids in septic shock
   i. In a study published in 2002, adult patients with septic shock were given a corticotropin stimulation test and then randomly assigned to intravenous hydrocortisone combined with oral fludrocortisone or placebo, regardless of stimulation test results. In the entire patient population, steroid therapy improved 28-day survival; however, this result was driven primarily by a mortality benefit in patients who were unresponsive to the corticotropin stimulation test.. Responders showed no improvement with steroid therapy (JAMA 2002;288:862-70).
   ii. The CORTICUS trial, published in 2008, had a similar method to the study above but omitted fludrocortisone. In this study, corticosteroids were not associated with a mortality benefit regardless of the results from a corticotropin stimulation test; however, they were associated with a higher risk of hyperglycemia, new sepsis, or septic shock. For this reason, corticosteroids are not recommended in patients with septic shock who have been stabilized with fluid and vasopressor therapy.
   iii. In the ADRENAL trial, published in 2018, adult patients with septic shock were randomized to receive an intravenous infusion of hydrocortisone or placebo. There was no difference in 90-day all cause mortality, but hydrocortisone infusion decreased duration of septic shock and blood transfusions. This is the largest randomized controlled trial assessing steroids in septic shock.
   iv. The APROCCHSS Trial, also published in 2018, had similar methods as the study from 2002 described above with intravenous hydrocortisone and oral fludrocortisone or placebo. There was a decrease in 90-day all cause mortality and duration of septic shock in patients treated with hydrocortisone and fludrocortisone.
   v. The mixed results from numerous studies leaves uncertainty as to the mortality benefit of steroid in septic shock. However, there seems to be consistency as to the short-term benefits including decreased time to resolution of shock.

e. Evidence-based guidelines
   i. SSC guidelines
      (a) The SSC recommends against using hydrocortisone to treat adults with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, the SSC suggests intravenous hydrocortisone alone at a dose of 200 mg per day.
      (b) The SSC recommends against using the corticotropin stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone.
      (c) Although fludrocortisone was a component of the treatment regimen in some studies, the SSC only includes hydrocortisone in recommendations for septic shock.
      (d) Of note, the ADRENAL and APROCCHSS trials were published in 2018 and are not included in the 2016 SSC guidelines.
   ii. American College of Critical Care Medicine corticosteroid insufficiency guidelines recognize that although hypothalamic-pituitary-adrenal axis dysfunction is common in some critically ill patients (sepsis), diagnosis and management of this disorder are complicated.
      (a) The expert panel's recommendations for septic shock are similar to the SSC guidelines, that hydrocortisone should be considered in the management strategy for patients with septic shock, particularly those who have responded poorly to fluid resuscitation and vasopressor agents.
      (b) Furthermore, the corticotropin stimulation test should not be used to identify patients with septic shock or acute respiratory distress syndrome (ARDS) who should receive glucocorticoids.
      (c) Patients should be weaned off steroid therapy once vasopressors are no longer necessary.

7. Metabolic resuscitation
    a. High-dose intravenous ascorbic acid (vitamin C) has anti-inflammatory and antioxidant properties that may be beneficial in sepsis.
    b. Thiamine deficiency occurs in critically ill patients with sepsis, and supplementation in these patients improves lactate clearance.
    c. Ascorbic acid and hydrocortisone may have synergistic protective effects on the vascular endothelium.
    d. A single-center, retrospective before-and-after study assessed coadministration of hydrocortisone, high-dose ascorbic acid, and thiamine (HAT) therapy for patients with severe sepsis or septic shock. HAT therapy was associated with a shorter duration of vasopressors and a 31.9% decrease in hospital mortality. However, other studies assessing hydrocortisone alone (described in the previous section) have consistently shown decreased time to resolution of septic shock and inconsistently shown improved mortality rates. Therefore, it is unclear whether the benefit was a result of HAT therapy or of hydrocortisone alone (Chest 2017;151:1229-38).
    e. Several randomized controlled trials were subsequently published that failed to reproduce the mortality benefit with HAT therapy. Although each trial had notable limitations, these trials suggest HAT therapy should not routinely be administered in sepsis. The VITAMINS trial included the largest patient cohort to date and compared HAT therapy with hydrocortisone alone. Results showed no improvement in the duration of time alive and free of vasopressor administration over 7 days (JAMA 2020;323:423-31).

III. INTERPRETATION OF ACID-BASE DISTURBANCES

A. Normal Arterial Blood Gas Values

pH	7.40 (range 7.35–7.45)
P_{CO_2}	35–45 mm Hg
P_{O_2}	80–100 mm Hg
HCO_3^-	22–26 mEq/L (or mmol/L)
Sa_{O_2}	95%–100%

B. Acidosis: Any pH less than 7.35 indicates a primary acidosis.

C. Alkalosis: Any pH greater than 7.45 indicates a primary alkalosis.

D. Metabolic disorders
    1. Acidosis: Decreased HCO_3^-
    2. Alkalosis: Increased HCO_3^-

E. Respiratory disorders
    1. Acidosis: Increased P_{CO_2}
    2. Alkalosis: Decreased P_{CO_2}

F. Compensation: Occurs in an attempt to normalize the pH in response to the primary problem (Table 5)
   1. Respiratory compensation occurs immediately with changes in respiratory rate.
      a. The compensation for metabolic acidosis is respiratory alkalosis (i.e., decrease in P_{CO_2}). This is achieved by increasing the respiratory rate to eliminate more CO_2, thus making pH more basic (i.e., higher pH).
      b. The compensation for metabolic alkalosis is a respiratory acidosis (i.e., increase in P_{CO_2}). This is achieved by slowing the respiratory rate to retain more CO_2, thus making pH more acidic (i.e., lower pH).
   2. Metabolic compensation occurs slowly in the kidneys by regulating the excretion and reabsorption of HCO_3^- and H^+.
      a. The compensation for a respiratory acidosis is metabolic alkalosis (i.e., an increase in HCO_3^-).
      b. The compensation for a respiratory alkalosis is metabolic acidosis (i.e., a decrease in HCO_3^-).

Table 5. Predicted Degrees of Compensation in Acid-Base Disturbances

Normal Values **HCO_3^- = 24 mmol/L** **P_{CO_2} = 40 mm Hg**	**Primary Disturbance**	**Compensation**
Metabolic acidosis	↓ HCO_3^- by 1 mmol/L	↓ P_{CO_2} by 1.2 mm Hg
Metabolic alkalosis	↑ HCO_3^- by 1 mmol/L	↑ P_{CO_2} by 0.7 mm Hg
Respiratory acidosis Acute Chronic (>3 days)	 ↑ P_{CO_2} by 10 mm Hg ↑ P_{CO_2} by 10 mm Hg	 ↑ HCO_3^- by 1 mmol/L ↑ HCO_3^- by 3.5 mmol/L
Respiratory alkalosis Acute Chronic (>3 days)	 ↓ P_{CO_2} by 10 mm Hg ↓ P_{CO_2} by 10 mm Hg	 ↓ HCO_3^- = 2 mmol/L ↓ HCO_3^- = 4 mmol/L

G. Steps to evaluate acid-base disorders (Table 6)
   1. Assess pH, P_{CO_2}, and HCO_3^-.
      a. Acidosis if pH less than 7.35
         i. If P_{CO_2} is elevated, the primary disorder is respiratory acidosis.
         ii. If HCO_3^- is decreased, the primary disorder is metabolic acidosis.
      b. Alkalosis if pH is greater than 7.45
         i. If P_{CO_2} is decreased, the primary disorder is respiratory alkalosis.
         ii. If HCO_3^- is elevated, the primary disorder is metabolic alkalosis.
   2. Calculate the anion gap (AG) = $[Na+] - [Cl^- + HCO_3^-]$.
      a. Normal range is 6–12 mEq/L.
      b. If AG is more than 12, there is a primary metabolic acidosis regardless of pH or HCO_3^-. Some patients have a mixed acid-base disorder in which they have more than one primary disorder.
      c. Hypoalbuminemia decreases the AG by 2.5–3 mEq/L for every 1-g/dL decrease in serum albumin less than 4 g/dL.
   3. Calculate the excess AG = Total AG − Normal AG. Add excess AG to serum bicarbonate.
      a. If the sum is greater than a normal serum bicarbonate (i.e., more than 30 mEq/L), there is also an AG metabolic alkalosis (this can occur in addition to other primary disorders).
      b. If the sum is less than a normal serum bicarbonate (i.e., less than 23 mEq/L), there is an underlying non-AG metabolic acidosis.

Table 6. Causes of Acid-Base Disturbances

	Respiratory Acidosis	Respiratory Alkalosis	Metabolic Acidosis	Metabolic Alkalosis
Etiology	Pulmonary edema Cardiac arrest CNS depression Stroke Pulmonary embolus Pneumonia Bronchospasm Spinal cord injury Sedatives	Anxiety Pain CNS tumor Stroke Head injury Hypoxia Stimulant drugs Reduced oxygen-carrying capacity Reduced alveolar oxygen extraction Respiratory rate stimulation Extracorporeal removal	**Anion gap** (MUDPILES) Methanol Uremia DKA Propylene glycol Intoxication or infection Lactic acidosis Ethylene glycol Salicylate **Non–anion gap** (F-USED CARS) Fistula (pancreatic) Uteroenteric conduits Saline excess Endocrine (hyperparathyroid) Diarrhea Carbonic anhydrase inhibitors Arginine, lysine, Cl^- Renal tubular acidosis Spironolactone	**Urine Cl^- > 25** (Chloride resistant) Hyperaldosteronism ↑ Mineralocorticoid **Urine Cl^- < 25** (Chloride responsive) Vomiting NG suction Diuretic
Treatment	Correct cause Invasive/noninvasive ventilation	Correct cause Oxygen supplementation Invasive/noninvasive ventilation Hypoventilation Sedation	Correct cause Use of bases (sodium bicarbonate or THAM) may be considered in non-AG metabolic acidosis Base use in AG metabolic acidosis is controversial (Sodium bicarbonate has traditionally been used, but evidence of clinical benefit is lacking)	Correct cause **If urine Cl^- > 25** Potassium Aldosterone antagonist Acetazolamide **If urine Cl^- < 25** 0.9% NaCl Consider acetazolamide Consider HCl (if severe)

AG = anion gap; Cl^- = chloride; CNS = central nervous system; DKA = diabetic ketoacidosis; HCl = hydrochloric acid; NaCl = sodium chloride; NG = nasogastric; THAM = tromethamine or tris-hydroxymethyl aminomethane.

Patient Cases

1. A 62-year-old woman has been hospitalized in the ICU for several weeks. Her hospital stay has been complicated by aspiration pneumonia and sepsis, necessitating prolonged courses of antibiotics. For the past few days, she has been having high temperatures again, and her stool output has increased dramatically. Her most recent stool samples have tested positive for *Clostridioides difficile* toxin, and her laboratory tests show serum sodium 138 mEq/L, potassium (K) 3.5 mEq/L, Cl 115 mEq/L, HCO_3^- 15 mEq/L, albumin 4.4 g/dL, pH 7.32, and $Paco_2$ 30 mm Hg. Which is most consistent with this patient's primary acid-base disturbance?
   A. AG metabolic acidosis.
   B. Non-AG metabolic acidosis.
   C. Chloride-responsive metabolic alkalosis.
   D. Acute respiratory acidosis.

2. A 32-year-old man with no pertinent medical history is admitted to the hospital after being "found down" in his home with an empty bottle of alprazolam by his side. On arrival at the emergency department, he was neurologically unresponsive, with the following ABG values: pH 7.21, partial pressure of carbon dioxide ($Paco_2$) 58 mm Hg, Pao_2 90 mm Hg, HCO_3- 24 mEq/L, and Sao_2 86% on 2 L/minute of oxygen by nasal cannula. Which action is most appropriate?
   A. Administer acetazolamide 500 mg intravenous push.
   B. Administer 100% oxygen by face mask.
   C. Give sodium bicarbonate 100 mEq intravenous push.
   D. Provide urgent intubation.

3. A 55-year-old woman is admitted to the hospital after several days of worsening shortness of breath. Recently, she was discharged from the hospital after a similar episode and was doing fine until 3 days before admission, when she developed a productive cough, necessitating an increase in her home oxygen and more frequent use of her metered dose inhalers. On admission to the medical ICU, she was anxious and markedly distressed, with rapid, shallow breaths. She was hypertensive (160/80 mm Hg), tachycardic (140 beats/minute), and tachypneic (respiratory rate 28 breaths/minute). Her ABG showed pH 7.30, $Paco_2$ 59 mm Hg, Pao_2 50 mm Hg, HCO_3- 28 mEq/L, and Sao_2 83% on 6 L/minute of oxygen by face mask, and she was immediately intubated. Her most recent laboratory tests show serum sodium 142 mEq/L, K 3.8 mEq/L, Cl 109 mEq/L, HCO_3- 28 mEq/L, and albumin 4.1 g/dL. Which primary acid-base disturbance is most consistent with this patient's presentation and laboratory data?
   A. AG metabolic acidosis.
   B. Non-AG metabolic acidosis
   C. Respiratory acidosis.
   D. Respiratory alkalosis.

Patient Cases *(Cont'd)*

4. A 65-year-old woman is admitted to cardiac surgery ICU after an aortic valve replacement. On hospital day 4, she is hypotensive (blood pressure 80/50 mm Hg), tachycardic (heart rate 125 beats/minute), tachypneic (respiratory rate 30 breaths/minute), hypoxemic (Pao_2 40 mm Hg), febrile (temperature 103.1°F [39.5°C]), and confused. The patient is given adequate boluses of lactated Ringer solution and is then reintubated and initiated on piperacillin/tazobactam 4.5 g intravenous piggyback every 6 hours and vancomycin 1000 mg intravenous piggyback every 12 hours for possible nosocomial pneumonia. After fluid boluses fail to improve her hemodynamic and clinical status, a pulmonary artery catheter is placed, which reveals a PCWP of 18 mm Hg, CI of 3.3 L/minute/m2 and SVR of 515 dynes/second/cm5. Her chest radiograph reveals a left lower lobe consolidation, and she still needs 100% fraction of inspired oxygen (Fio_2). Which action is best?

   A. Administer angiotensin II infusion titrated to achieve a MAP of at least 65 mm Hg.

   B. Administer a dobutamine infusion titrated to achieve a MAP of at least 65 mm Hg.

   C. Administer a norepinephrine infusion titrated to achieve a MAP of at least 65 mm Hg.

   D. Administer a dopamine infusion titrated to achieve a MAP of at least 65 mm Hg.

5. A patient (weight 75 kg) is to be initiated on a continuous infusion of norepinephrine for blood pressure support because of septic shock. The nurse has a 250-mL bag of normal saline containing 4 mg of norepinephrine. Which rate is most appropriate to infuse the norepinephrine drip at a dose of 0.05 mcg/kg/minute?

   A. 7 mL/hour.

   B. 14 mL/hour.

   C. 31.5 mL/hour.

   D. 79 mL/hour.

6. A 42-year-old man was found unresponsive at his group home covered in vomit. He was intubated by the paramedics. On arrival at the emergency department, his blood pressure is 72/30 mm Hg and heart rate is 95 beats/minute. During the next few hours, he receives 5 L of lactated Ringer solution, 500 mL of 5% albumin, and norepinephrine infusing at 0.5 mcg/kg/minute. With these interventions, his blood pressure is 87/56 mm Hg and heart rate is 148 beats/minute. Pertinent laboratory values include WBC 20×10^3 cells/mm^3, lactic acid 1.5 mmol/L, aspartate aminotransferase 78 units/L, SCr 2.2 (baseline 1) mg/dL, platelet count 118,000 cells/mm^3, international normalized ratio (INR) 1.4, and urine output about 45 mL/hour since arrival. Which is the most appropriate intervention at this time?

   A. Add hydrocortisone 50 mg intravenously every 6 hours.

   B. Change norepinephrine infusion to phenylephrine infusion.

   C. Change norepinephrine infusion to dopamine infusion.

   D. Administer 1 L of lactated Ringer solution.

IV. CARDIAC ARREST

A. Training: Any pharmacist who participates in codes should complete basic life support (BLS) and advanced cardiac life support (ACLS) training. In general, BLS training takes 3–5 hours to complete, and ACLS training takes 2 days. The information presented in this section consists of selected highlights from these training sessions; it should not be used in place of a comprehensive training program.

B. 2015 American Heart Association (AHA) Guidelines
   1. Medications used during ACLS: See "Acute Care in Cardiology" chapter for information on drugs, indications, and dosages.
   2. CAB (compressions, airway, breathing): In an unresponsive patient or a patient who is not breathing, one rescuer should initiate a cycle of 30 chest compressions as soon as possible, followed immediately by 2 rescue breaths. After placement of an advanced airway, it may be reasonable for the provider to deliver 1 breath every 6 seconds (10 breaths/minute) while continuous chest compressions are being performed.
   3. Emphasis is on high-quality cardiopulmonary resuscitation (CPR), with a compression rate of 100–120 compressions/minute at a depth of at least 2 inches and allow complete chest recoil.
   4. For ventricular fibrillation or pulseless ventricular tachycardia, electrical therapy (by an automated external defibrillator or defibrillator) should be initiated as soon as it is available.
   5. Interruptions in chest compressions should be minimal and and no longer than 10 seconds. Chest compressions and defibrillation should not be interrupted for vascular access, medication administration, or airway placement.
   6. End-tidal carbon dioxide ($EtCO_2$) is the partial pressure of exhaled carbon dioxide at the end of expiration. It is measured using waveform capnography. During cardiac arrest, $EtCO_2$ levels reflect the cardiac output generated by chest compressions and myocardial blood flow. $EtCO_2$ levels less than 10 mm Hg immediately after intubation and 20 minutes after initial resuscitation are associated with poor chances of ROSC and survival.
   7. Medication administration
      a. Central venous administration is preferred.
      b. If medications are administered through a peripheral vein, it is important to follow the medication with 20 mL of intravenous fluid to facilitate drug flow from the extremity to the central circulation.
      c. Intraosseous administration is preferred to endotracheal administration if intravenous administration is not possible because of its more predictable drug delivery and pharmacologic effect.
      d. Endotracheal drug administration can be performed by administering 2–2.5 times the standard intravenous dose and diluting in 5–10 mL of sterile water. The following drugs can be administered through an endotracheal tube: naloxone, atropine, vasopressin, epinephrine, lidocaine.

C. Post–cardiac arrest care
   1. After ROSC, systematic post–cardiac arrest care can improve survival and quality of life.
   2. Initial therapy should optimize ventilation, oxygenation, and blood pressure.
      a. Sao_2 should be maintained at 94% or higher.
         i. Insertion of an advanced airway may be necessary.
         ii. Hyperventilation and excess oxygen delivery are harmful and should be avoided, especially after ROSC.
      b. Hypotension (SBP of 90 mm Hg or less) should be treated with fluid boluses and vasopressors if necessary.
   3. Avoidance of hyperthermia is recommended because fever in patients after cardiac arrest is associated with poor neurologic outcomes.

4. Targeted temperature management (therapeutic hypothermia)
    a. Induction of hypothermia (32°C–36°C) for at least 24 hours beginning as soon as possible after ROSC can improve neurologic recovery and mortality. The AHA guidelines recommend that all comatose adult patients with ROSC have targeted temperature management. One study (N Engl J Med 2013;369:2197-206) has shown that a standard target temperature (33°C) does not confer a benefit over a higher target temperature (36°C). A recent single-center, retrospective, before-and-after cohort study showed that 33°C was associated with a 79% increased odds of neurologically intact survival to discharge compared with 36°C but no difference in hospital mortality. However, those in the 33°C group were cooled faster (1.9 hours vs. 3.5 hours, $p<0.001$), which is a notable limitation that may have affected the results (Crit Care Med 2020;48:362-9). The AHA guidelines allow the clinician to select the exact target temperature.
    b. No single method for inducing hypothermia is recommended over another. Surface cooling devices, endovascular catheters, cooling blankets, ice packs, and cold intravenous fluids can be used.
    c. Core temperature should be monitored continuously.
    d. Many patients will need sedation and analgesia during periods of hypothermia.
    e. Rewarming should be done slowly (0.3°C–0.5°C every hour), and patients should remain afebrile.
    f. Complications
        i. Shivering
            (a) Shivering causes excess heat production, increased oxygen consumption, and a general stress response; it should be treated and prevented.
            (b) Shivering can be treated with sedatives (dexmedetomidine, ketamine), anesthetics, analgesics (e.g., meperidine, fentanyl, tramadol), dexamethasone, clonidine, magnesium, ondansetron, buspirone, and paralytics (please see Crit Care Med 2012;40:3070-82 for individual drugs and doses).
            (c) Note that shivering can be treated without the use of paralytics in many patients. Therefore, paralytics are not mandatory and should be avoided if possible (see disadvantages of paralytics in section VI: Pain, Agitation, Delirium, and Neuromuscular Blockade). Paralytics may be most beneficial during the induction of hypothermia and during rewarming (when risk of shivering is greatest); however, they should be continually reevaluated and discontinued, if possible, once goal temperature is achieved.
        ii. Altered drug metabolism
            (a) Drug clearance is typically reduced during hypothermia, including a depressed activity of cytochrome P450 (CYP) 3A4 and 3A5 hepatic enzymes. Hypothermia can also affect the distribution of drugs to their site of action (e.g., propofol). These effects become more pronounced at cooler temperatures.
            (b) Use bolus dosing during the induction of hypothermia.
            (c) Reduce maintenance doses of sedatives (e.g., midazolam, propofol), opiates (fentanyl, remifentanil), phenobarbital, phenytoin, paralytics, and other drugs as needed (see review article Crit Care Med 2007;35:2196-204).
        iii. Coagulopathy
            (a) Providers may choose not to cool patients with preexisting coagulopathy because of the increased risk of bleeding.
        iv. Increased renal excretion of water and subsequent volume depletion
        v. Arrhythmia and hypotension
            (a) Usually bradycardia
            (b) Discontinue or slightly warm patient if life-threatening arrhythmias or persistent hemodynamic instability develops.

vi. Hyperglycemia and hypoglycemia
    (a) Hyperglycemia during hypothermia, hypoglycemia during rewarming.
    (b) Monitor blood glucose often (i.e., every 1–2 hours) and adjust insulin accordingly.
vii. Infection
viii. Electrolyte disturbances
    (a) Reductions in K, magnesium, and phosphate during cooling
    (b) Hyperkalemia during rewarming
    (c) Special electrolyte replacement protocols should be used to ensure that patients do not receive too much potassium during cooling such that they are hyperkalemic during rewarming. Electrolyte shifts occur during the induction and rewarming phases of TTM. Frequent monitoring and careful repletion is important to prevent complications from electrolyte abnormalities.

Patient Case

7. A 61-year-old woman collapses in front of her family members, who call 9-1-1 and begin CPR. The paramedics arrive and find the victim unresponsive, with an electrocardiogram revealing ventricular fibrillation, and administer two additional rounds of CPR and two defibrillations, which are successful. In the emergency department, the patient's MAP is 68 mm Hg after fluids and norepinephrine, but the patient remains unresponsive. She is initiated on the hypothermia protocol. After 24 hours of hypothermia (body temperature 33°C), the patient is in the ICU, and the rewarming process has recently begun. The pharmacist arrives in the ICU about 30 minutes into the rewarming process. The patient has been receiving a continuous infusion of insulin throughout the period of hypothermia at an average rate of 4 units/hour, with blood glucose testing every 3 hours. The patient has been sedated with a continuous infusion of propofol and fentanyl and is receiving cisatracurium for neuromuscular blockade. The patient's vital signs are stable, and her laboratory values are normal. Which pharmacist recommendation is most appropriate at this time?

    A. Increase blood glucose testing to now and every 1–2 hours during rewarming.

    B. Adjust cisatracurium infusion to achieve a TOF of 0/4 impulses.

    C. Discontinue propofol infusion to facilitate extubation.

    D. Increase insulin infusion to prevent hyperkalemia.

V. ACUTE RESPIRATORY FAILURE

A. Causes of respiratory failure (Table 7)

Table 7. Respiratory Failure

Indication for Mechanical Ventilation	Examples
Hypoventilation (hypercapnic respiratory failure)	Drug overdose Neuromuscular disease Cardiopulmonary resuscitation Central nervous system injury or disease
Hypoxemia (hypoxic respiratory failure)	Pulmonary injury or disease Pneumonia Pulmonary edema Pulmonary embolus Acute respiratory distress syndrome
Inability to maintain airway	Loss of airway patency (mechanical obstruction, tracheal or chest wall injury) Loss of gag or cough reflex with large-volume aspiration risk (e.g., central nervous system injury, central nervous system depression, cardiovascular accident, seizures, cardiac arrest)

B. Complications associated with mechanical ventilation (see individual sections later in text for prevention of these complications)
   1. Ventilator-associated pneumonia
   2. Stress ulcers
   3. Venous thrombosis

VI. PAIN, AGITATION, DELIRIUM, AND NEUROMUSCULAR BLOCKADE

A. General considerations
   1. Nonpharmacologic strategies to improve patient comfort include lighting, music, massage, verbal reassurance, avoidance of sleep deprivation, and patient positioning based on patient preferences.
   2. Determine patient goals using validated scales and routinely assess pain and sedation.
      a. Routine assessment of pain and sedation should be performed in every patient in the ICU.
         i. Self-reporting is preferred to pain scales for assessing pain in patients who are able to communicate.
         ii. To assess pain in patients who are unable to communicate, the Behavioral Pain Scale (BPS; Table 8) and the Critical-Care Pain Observation Tool (CPOT; Table 9) are recommended because, compared with other scores, they are more valid and reliable for monitoring pain in adult patients in the ICU (except those with brain injury).
            (a) The total BPS score can range from 3 (no pain) to 12 (maximum pain). A score of 6 or higher is generally considered to reflect unacceptable pain.
            (b) The total CPOT score can range from 0 to 8. A score of 3 or higher is generally considered to reflect unacceptable pain.

Table 8. The Behavioral Pain Scale

Item	Description	Score
Facial expression	Relaxed Partially tightened (e.g., brow lowering) Fully tightened (e.g., eyelid closing) Grimacing	1 2 3 4
Upper limb movements	No movement Partially bent Fully bent with finger flexion Permanently retracted	1 2 3 4
Compliance with mechanical ventilation	Tolerating movement Coughing but tolerating ventilation for most of the time Fighting ventilator Unable to control ventilation	1 2 3 4

Adapted from: Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.

Table 9. Critical Care Pain Observation Tool

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral: 0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense: 1
	All the above facial movements plus eyelids tightly closed	Grimacing: 2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movement: 0
	Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements	Protection: 1
	Pulling tube, trying to sit up, moving limbs or thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness: 2
Muscle tension	No resistance to passive movements	Relaxed: 0
	Resistance to passive movements	Tense, rigid: 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid: 2
Compliance with the ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement: 0
	Alarms stop spontaneously	Coughing but tolerating: 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator: 2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound: 0
	Sighing, moaning	Sighing, moaning: 1
	Crying out, sobbing	Crying out, sobbing: 2

Adapted from: Gélinas C, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care 2006;15:420-7.

iii. Vital signs (e.g., elevated heart rate or blood pressure) indicate further assessment of pain is necessary in patients who are receiving neuromuscular blockade.

iv. To assess sedation, the Richmond Agitation-Sedation Scale (RASS; Table 10) and Sedation-Agitation Scale (SAS; Table 11) are recommended because, compared with other sedation scores, they are more valid and reliable for monitoring the quality and depth of sedation in adult ICU patients. Goal sedation scores should be individualized for each patient, but generally, a RASS score of 0 to -1 or an SAS score of 3 or 4 is recommended.

Table 10. Richmond Agitation-Sedation Scale

Scale	Term	Description
+4	Combative	Combative, violent, immediate danger to staff members
+3	Very agitated	Pulls to remove tubes or catheters; aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive
0	Alert and calm	Spontaneously pays attention to caregiver
–1	Drowsy	Not fully alert but has sustained awakening to voice (eye opening and eye contact for ≥10 s)
–2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
–3	Moderate sedation	Movement or eye opening to voice but no eye contact
–4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

Information from: Pun B, Dunn J. The sedation of critically ill adults: part 1. Assessment. Am J Nurs 2007;107:40-8.

Table 11. Sedation-Agitation Scale

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative	Calm, easily roused, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Information from: Pun B, Dunn J. The sedation of critically ill adults: part 1. Assessment. Am J Nurs 2007;107:40-8.

b. Pain and discomfort are primary causes of agitation; therefore, treat pain first and add a sedative if needed. This is often referred to as analgosedation.
   i. Use bolus dose analgesics and/or nonpharmacologic interventions before potentially painful procedures.
   ii. Opioid analgesics are considered first line for the treatment of nonneuropathic pain. Gabapentin or carbamazepine can be considered for neuropathic pain. However, gabapentin is typically preferred because of the adverse effects and drug interactions associated with carbamazepine.
   iii. Nonopioid analgesics (e.g., acetaminophen, ketamine) can be used in conjunction with opioids as a "multimodal analgesia" approach to optimize pain control and to avoid dose-related adverse effects.
   iv. Nonsteroidal anti-inflammatory drugs are usually avoided because of the risk of bleeding and kidney injury in critically ill patients.
   v. Nonbenzodiazepine sedatives may be preferred to benzodiazepines to improve clinical outcomes in mechanically ventilated patients.

c. Dosing strategies for analgesics and sedatives
   i. Analgesics and sedatives should be dosed to achieve pain and sedation goals. Adjust sedative medications to achieve a light level of sedation (RASS 0 to –1). Light sedation is needed for evaluating pain and delirium and for early patient mobility.
   ii. Goals can be achieved using intermittent dosing administered routinely or as needed.
   iii. If unable to achieve goals with intermittent dosing, use a combination of bolus dosing with a continuous infusion.
      (a) In patients receiving a continuous infusion, use a bolus dose before or instead of increasing the infusion rate (a bolus dose has a faster onset and can eliminate the need for an increase in the infusion rate). An exception is with drugs such as propofol or dexmedetomidine, which can cause hypotension or bradycardia when bolused.
      (b) Use bolus dosing proactively (e.g., before dressing changes, suctioning, repositioning).
   iv. Daily awakening involves an interruption of continuous infusion opioid or sedatives until the patient is awake (SAS score of at least 4 or RASS score of at least 0) or shows discomfort or pain necessitating reinitiation, ideally at a reduced dose. Although evidence is mixed, a scheduled daily interruption of continuous infusions is associated with several important benefits.
      (a) Assess the patient's neurologic function.
      (b) Reevaluate lowest effective opioid or sedative dose.
      (c) Prevent drug accumulation and overdose.
      (d) Reduce time on the ventilator (although one randomized study contradicts this by finding no reduction in the duration of mechanical ventilation or ICU stay with sedation interruption; JAMA 2012;308:1985-92).
      (e) Reduce mortality and ICU length of stay when combined with a spontaneous breathing trial.
      (f) Reduce symptoms of posttraumatic stress disorder and post-ICU syndrome.

B. Analgesics (Table 12)

Table 12. Intravenous Analgesics

	Morphine	Fentanyl	Hydromorphone
Pharmacokinetics			
Onset (min)	5–10	1–2	5–15
Duration of effect (hr)	2–4	1–5	2–6
Prolonged in renal failure	Yes	No	No
Prolonged in hepatic failure	Yes	Yes	Yes
Elimination half-life (hr)	3–4	2–4	2–3
Active metabolites	Yes	No	No
Adverse effects			
Hypotension	Yes	No	Yes
Flushing	Yes	No	Yes
Bronchospasm	Yes	No	No
Constipation	Yes	Yes	Yes

C. Sedatives
   1. Guidelines suggest using propofol or dexmedetomidine over benzodiazepines for sedation in mechanically ventilated adult patients. Benzodiazepines should be avoided when possible to prevent adverse outcomes, including prolonged duration of mechanical ventilation, increased ICU length of stay, and development of delirium (Table 13).
   2. Lorazepam
      a. Intermittent dosing 1–4 mg every 2–6 hours
      b. Continuous infusion: Start at 1 mg/hour and titrate to goal (e.g., RASS, SAS). Total daily doses as low as 1 mg/kg can cause propylene glycol toxicity. If high-dose continuous infusion is used, monitor for an osmolal gap greater than 10–12 mOsm/L, indicating propylene glycol toxicity.
      c. Lorazepam is the preferred benzodiazepine in severe hepatic dysfunction because of its metabolism.
   3. Midazolam
      a. Intermittent dosing 1–4 mg every 15 minutes to 1 hour
      b. Continuous infusion: Start at 1 mg/hour and titrate to goal (e.g., RASS, SAS).
      c. Often used for procedural sedation or daily dressing changes because of its rapid onset and short duration
      d. Prolonged infusions of midazolam may accumulate because of its greater lipophilicity and active metabolites compared with lorazepam, especially in patients with renal dysfunction.
   4. Diazepam
      a. Not routinely used as a sedative for mechanically ventilated patients because of accumulation of active metabolites with prolonged administration.
      b. Often used for the treatment of alcohol withdrawal because of its rapid onset and long half-life.

Table 13. Intravenous Benzodiazepines

	Diazepam	Lorazepam	Midazolam
Pharmacokinetics			
Onset (minutes)	2–5	15–20	2–5
Duration of effect (hr)	2–4	4–6	1–2
Prolonged in renal failure	Yes	No	Yes
Prolonged in hepatic failure	Yes	No	Yes
Elimination half-life (hr)	24–120	10–20	1–10
Active metabolite	Yes	No	Yes
CYP3A4 interactions	Yes	No	Yes
Adverse effects			
Hypotension	Yes	No	No
Thrombophlebitis	Yes	Maybe	No
Propylene glycol toxicity	No	Yes	No

CYP = cytochrome P450.

   5. Propofol
      a. Rapid onset (1–2 minutes) and short duration (3–5 minutes or longer if prolonged infusion)
      b. Initiate at 5 mcg/kg/minute and titrate to achieve sedation goals by 5 mcg/kg/minute every 5 minutes. Avoid prolonged infusions greater than 80 mcg/kg/minute because of the patient's risk of developing propofol-related infusion syndrome.
      c. Avoid loading doses because of the risk of hypotension.
      d. In general, used in intubated patients because of the risk of respiratory depression

e. Propofol has no significant analgesic activity. If a patient has pain, propofol must be combined with an analgesic.
f. Monitoring
    i. Blood pressure
    ii. Triglyceride concentrations should be obtained when propofol is administered for at least 48 hours or at a rate of at least 50 mcg/kg/minute. An alternative agent should be given if severe hypertriglyceridemia occurs because the patient's risk of developing pancreatitis increases.
    iii. Calories provided from 10% lipid emulsion (1.1 kcal/mL). May need to adjust lipid or calories provided by nutrition support (i.e., EN or PN)
    iv. Propofol-related infusion syndrome is more likely to occur with infusion rates of at least 80 mcg/kg/minute for at least 48 hours, and is associated with metabolic acidosis, cardiac failure, arrhythmias (e.g., bradycardia), cardiac arrest, rhabdomyolysis, hyperkalemia, and kidney failure.
g. Propofol is more commonly used than benzodiazepines because of its shorter duration, easy titration, and predictability.

6. Dexmedetomidine
    a. Sedative properties through central and peripheral α_2-receptor agonist activity
    b. Extent of analgesic activity in patients in the ICU is not well described.
    c. Does not cause respiratory depression
    d. Rapid onset (5–15 minutes if bolus, longer without bolus) and short duration (2-hour half-life). Longer duration in patients with severe hepatic dysfunction
    e. A loading dose is suggested for patients undergoing surgery; however, loading doses are not recommended for patients in the ICU because of the risk of bradycardia and hypotension.
    f. Maintenance dose of 0.2–0.7 mcg/kg/hour is approved by the U.S. Food and Drug Administration for a maximum of 24 hours; however, there is evidence showing the safety and efficacy of prolonged infusions at doses of up to 1.5 mcg/kg/hour, and this is most commonly used in practice.
    g. Compared with benzodiazepines, dexmedetomidine is associated with a lower prevalence of ICU delirium in some studies.
    h. Results from the MIDEX and PRODEX studies show that dexmedetomidine is noninferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine reduced the duration of mechanical ventilation compared with midazolam but was noninferior compared to propofol (JAMA 2012;307:1151-60).
    i. Monitoring: Primary adverse effects are dose-related bradycardia and hypotension.
    j. Does not cause drug dependency, but withdrawal symptoms (e.g., nausea, vomiting, agitation) have occurred after prolonged use (1 week).
7. Ketamine
    a. *N*-methyl-D-aspartate receptor antagonist
    b. Has both analgesic and sedative properties
    c. Does not cause respiratory depression
    d. Dosing and titration strategies vary widely by institution.
    e. Risk of emergence delirium when high doses are tapered off. It is unclear whether benzodiazepines will reduce the risk of emergence.
    f. Major adverse effects include hypertension, tachycardia, and delirium.
    g. Has been associated with an opioid-sparing effect, especially in patients with chronic pain
    h. Guidelines suggest using low-dose ketamine as an adjunct to opioid therapy when seeking to reduce opioid use in postsurgical patients. There is no routine use for ketamine in sedation or in prevention and treatment of delirium.

D. Assessment and management of delirium
   1. Delirium is an acute change in cognitive function characterized by disorganized thought, altered level of consciousness, and inattentiveness.
   2. Delirium is associated with increased mortality, prolonged length of stay in the ICU, and cognitive impairment after ICU discharge.
   3. Validated tools to proactively identify and assess delirium include the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). The CAM-ICU is designed to detect delirium at the time of testing, whereas the ICDSC detects delirium during a nursing shift. For a detailed description of delirium monitoring tools, see http://icudelirium.org/delirium/monitoring.html.
   4. Nonpharmacologic interventions are preferred to pharmacologic treatment. These interventions include maintaining communication with the patient, reorienting the patient (to person, place, and time), maximizing uninterrupted sleep (e.g., control light and noise, cluster patient care activities, decrease stimuli at night), providing access to natural lighting (rooms with windows), removing unnecessary equipment from room, correcting sensory deficits (e.g., hearing aids, glasses), removing unneeded invasive devices (e.g., urinary catheters, intravenous lines, endotracheal tubes, enteral feeding tubes), minimizing physical restraint, and encouraging patient autonomy and early mobility.
   5. Correctable causes of delirium include hypotension, hypoxia, and electrolyte disturbances.
   6. Few interventions have been shown to improve delirium-related outcomes; therefore, a strong focus should be put on minimizing or treating reversible risk factors such as avoiding or minimizing the dose of benzodiazepines and other medications that can cause delirium (e.g., opioids, anticholinergic medications).
   7. Guidelines discourage routine use of antipsychotics for the treatment of delirium. However, they should be considered when patients experience significant distress because of symptoms of delirium. Antipsychotics should be used as a short treatment until symptoms resolve.

E. Pharmacologic treatment of delirium (Table 14)
   1. Haloperidol
      a. Although commonly used, there is no evidence that haloperidol reduces the duration of delirium.
      b. Monitoring
         i. Hypotension
         ii. Assess QTc interval at baseline and daily during haloperidol administration. In addition, monitor for other drugs that could prolong QTc interval. Prolongations of greater than 500 milliseconds are associated with a higher risk of torsades de pointes.
         iii. Extrapyramidal effects, including laryngeal dystonia and dysphagia, are more common with chronic oral administration than with intravenous administration.
      c. Lower initial doses of haloperidol (1–2.5 mg) should be used in older adults because of greater risks of adverse effects, including QTc prolongation.
      d. Doses of haloperidol for acute agitation can be doubled every 20 minutes until an effective dose is reached.
   2. Atypical antipsychotics
      a. Atypical or second-generation antipsychotics can reduce the duration of delirium in critically ill patients.
      b. Atypical antipsychotics are associated with a lower incidence of extrapyramidal symptoms (EPSs) than is haloperidol.
      c. Differences between agents are half-life, the risk of QTc prolongation, sedation, and risk of EPSs.
         i. Sedative effects may or may not be beneficial (e.g., hyperactive vs. hypoactive delirium).
         ii. Agents with a shorter half-life (quetiapine) generally act faster and can be quickly titrated.
         iii. Olanzapine and risperidone have less risk of QTc prolongation but should still be monitored.

Table 14. Medications Used to Treat Delirium

Medication	Initial Dosing	Dose Forms	Half-life (hr)	Adverse Effects
Haloperidol	2.5 mg every 6 hr	Tablet, IM, IV	18	QTc prolongation EPSs
Quetiapine	25 mg twice daily	Tablet	6	Sedation QTc prolongation
Olanzapine	5 mg daily	Tablet, ODT, IM	33	Sedation QTc prolongation (less than other agents)
Risperidone	0.5 mg twice daily	Tablet, ODT, solution, IM[a]	24	EPSs (doses > 6 mg/day) QTc prolongation (less than other agents)
Ziprasidone	20 mg twice daily	Capsule, IM	7	Sedation QTc prolongation

[a]IM formulation of risperidone is a long-acting formulation that is not indicated for acute delirium management.
EPS = extrapyramidal symptom; IM = intramuscular(ly); IV = intravenous(ly); ODT = orally disintegrating tablet.

F. Neuromuscular blockade in patients in the ICU (Table 15)
   1. Neuromuscular blockade is typically indicated for intubated patients with severe respiratory failure (e.g., ARDS, status asthmaticus) despite optimization of analgesia, sedation, and ventilator management.
   2. In patients with severe ARDS (defined as a PaO_2/Fio_2 ratio less than 150), a 48-hour infusion of cisatracurium (15-mg bolus followed by 37.5 mg/hour for 48 hours) showed a decreased adjusted 90-day mortality (N Engl J Med 2010;363:1107-16). More recent data analyses using a similar regimen had conflicting results with no difference in mortality or ICU-related weakness, but increased adverse cardiovascular events (N Engl J Med 2019;380:1997-2008). Notable differences between these studies (e.g., the degree of sedation in the control group and differences in use of prone positioning) may have contributed to the discrepancy. Of note, in these studies, the cisatracurium infusion was a fixed dose and was not adjusted on the basis of the monitoring parameters described later (e.g., TOF). Because of the lack of a clear benefit in ARDS, neuromuscular blockers should be reserved for patients with additional indications for use (e.g., severe ventilator dyssynchrony).
   3. Neuromuscular blockers are also used as adjunctive agents to control severe intracranial hypertension in patients with neurologic injury (e.g., traumatic brain injury).
   4. Neuromuscular blockers are typically used once efforts to facilitate ventilation have failed (e.g., poor oxygenation, dyssynchrony, high intrathoracic pressures that put the patient at risk for barotrauma) and a combination of high-dose opioids and sedatives have failed (i.e., patient continues to have poor oxygenation).
   5. Neuromuscular blockers may be used to attenuate shivering during therapeutic hypothermia.
   6. Never use neuromuscular blockers in a patient who is not completely sedated or does not have adequate pain control.
   7. Neuromuscular blockers should be used only in conjunction with a continuously infused sedative. Sedatives should have amnestic properties (e.g., benzodiazepines, propofol). Analgesics can also be used as needed in patients with pain. Dexmedetomidine does not provide the depth of sedation required for neuromuscular blocker infusion. Many practitioners insist on the combination of a sedative and an analgesic in paralyzed patients. Patients should be provided with lubricating eye drops while paralyzed.
   8. Neuromuscular blockade in the ICU can be used in cases of elevated ICP, tetanus, or intubation and to decrease movement during procedures.

Table 15. Neuromuscular Blocking Agents

Recommendation	Pancuronium	Vecuronium	Atracurium	Cisatracurium
Duration of effect (hr)	0.75–1.5	0.5–0.75	0.25–0.5	0.5–1
Prolonged in renal failure	Yes	Yes	No	No
Prolonged in hepatic failure	Yes	Yes	No	No
Loading dose	0.08 mg/kg	0.1 mg/kg	0.4 mg/kg	0.1 mg/kg
Maintenance dose	0.8-1.7 mcg/kg/min	0.8-1.7 mcg/kg/min	4-20 mcg/kg/min	2–10 mcg/kg/min
Adverse effects				
Tachycardia	Yes	No	No	No
Hypotension	No	No	Dose-dependent	No

9. Concerns with neuromuscular blockade
    a. Can mask seizure activity
    b. Prolonged use is associated with critical illness poly-neuromyopathy, which is characterized by prolonged muscle weakness.
    c. Can mask insufficient analgesia and sedation
    d. Increased risk of VTE
    e. Increased risk of skin breakdown and decubitus
    f. Corneal abrasions caused by eye dryness and lack of blinking; prevent by applying ophthalmic ointment or drops to eyes every 6–8 hours
10. Monitoring
    a. Neuromuscular blockers must be monitored to prevent an excessive degree of blockade and prolonged paralysis.
    b. The goal of neuromuscular blockade is to facilitate safe and optimal mechanical ventilation strategies using the minimal degree of neuromuscular blockade needed.
    c. Even with appropriate individualized dosing and monitoring of neuromuscular blockade, a principal adverse effect is prolonged muscle weakness after discontinuation. This can dramatically slow patient recovery, increasing the need for health care resources (e.g., physical therapy, rehabilitation). For this reason, it must be emphasized that the need for therapeutic paralysis must be carefully considered and reevaluated every day.
    d. A simple way to assess the appropriateness of the paralytic is as follows. Regularly (e.g., once daily) but temporarily discontinue the drug to determine the time needed for the patient to move or breathe spontaneously. Although not applicable to all patients, this "drug holiday" can be useful for the following reasons:
        i. Assess sedation and adjust sedatives as needed (e.g., if the patient is agitated after the drug is discontinued, he or she is not receiving adequate sedation or analgesia).
        ii. Assess the need for continued blockade (e.g., if the patient can maintain oxygenation, then perhaps the drug is no longer necessary).
        iii. Assess the dose of the paralytic (e.g., determine whether the paralysis wore off within the expected time according to the expected drug duration); this is especially important for drugs such as vecuronium because of the long half-life and dependence on end organ clearance.
        iv. Note that the studies listed earlier (N Engl J Med 2010;363:1107-16; N Engl J Med 2019;380:1997-2008) used cisatracurium continuously (without a holiday) for 48 hours without an increased incidence of prolonged weakness.

e. A peripheral nerve stimulator can be used in conjunction with drug holidays to assess the level of neuromuscular blockade and guide drug dosing.
   i. The TOF refers to peripheral nerve stimulation using four electrical impulses, usually applied to the ulnar or facial nerves.
   ii. Obtain a baseline TOF before initiation to determine patient sensitivity to impulses. Patients who are not blocked should have one twitch for each impulse (for 4/4 twitches).
   iii. During neuromuscular blockade infusions for respiratory failure, patients should typically be maintained at one or two twitches, which indicates 85%-90% receptor blockade.
   iv. Technical problems that limit the accuracy of TOF monitoring include the presence of perspiration or tissue edema. The TOF monitor may no longer be accurate if the electrodes are moved after the neuromuscular blocker is initiated.

11. In addition to the monitoring described, clinical assessment involves adjusting the neuromuscular blocker dose to prevent patient-ventilator dyssynchrony (e.g., "bucking" the ventilator, elevated peak airway pressures).
12. Avoid other medications or electrolyte abnormalities that can potentiate or inhibit paralysis (Table 16).

Table 16. Interactions with Neuromuscular Blockers

	Potentiate Block	**Antagonize Block**
Drugs	Corticosteroids Aminoglycosides Clindamycin Tetracyclines Polymyxins Calcium channel blockers Type Ia antiarrhythmics Furosemide Lithium	Aminophylline Theophylline Carbamazepine Phenytoin (chronic)
Electrolyte disorders	Hypermagnesemia Hypocalcemia Hypokalemia	Hypercalcemia Hyperkalemia

Patient Cases

8. An older woman is admitted to the ICU for acute decompensated heart failure and acute kidney injury with an ejection fraction of less than 30%. She is administered a continuous infusion of bumetanide; however, the benefit is limited because of her acute-on-chronic kidney disease. She is intubated on ICU day 2 because of worsening pulmonary edema and hypoxia. After intubation, her RASS score is 0, her CAM-ICU is negative, and her CPOT score is 4. Her blood pressure is 120/70 mm Hg and heart rate is 88 beats/minute. Which is the best recommendation for achieving her analgesia, sedation, and delirium goals?

   A. Initiate propofol at 5 mcg/kg/minute and titrate as needed.

   B. Administer haloperidol 5 mg intravenously as needed.

   C. Administer fentanyl 25 mcg intravenously every hour as needed.

   D. Initiate lorazepam 2 mg/hour and titrate as needed.

Patient Cases *(Cont'd)*

Questions 9–11 pertain to the following case.

A 42-year-old woman with ARDS and a significant history of alcohol and tobacco abuse is transferred to the medical ICU from an outside hospital. She presented to the outside hospital after 1 week of productive cough, fever, chills, and increased shortness of breath. On admission to the medical ICU, she is hypotensive (80/60 mm Hg), tachycardic (130 beats/minute), and febrile (body temperature 102.2°F [39.0°C]). Her ABG shows pH 7.1, $Paco_2$ 56 mm Hg, Pao_2 49 mm Hg, HCO_3^- 16 mEq/L, and Sao_2 76% on 100% Fio_2. The only other significant laboratory results are SCr 2.1 mg/dL and WBC 16×10^3 cells/mm^3. She is achieving her sedation goals with continuous infusions of propofol 20 mcg/kg/minute and fentanyl 200 mcg/hour.

9. After several nonpharmacologic attempts to improve her oxygenation fail, she is paralyzed, and her ventilator settings are adjusted accordingly. Which statement about neuromuscular blockade in this patient is most appropriate?
   A. Opioids should be discontinued to avoid prolonged neuromuscular weakness.
   B. Vecuronium is the agent of choice.
   C. Sedatives should be titrated to maintain an RASS goal of 0 to –2 during neuromuscular blockade.
   D. Neuromuscular blockers should be titrated to the minimal dose necessary to achieve ventilator synchrony.

10. The patient was initiated on neuromuscular blockade as instructed and synchronous with the ventilator, but about 8 hours later, she began to move around violently in her bed. At this time, she was tachycardic (heart rate 120 beats/minute) and appeared agitated; her Sao_2 dropped to 80%. Which action is best?
   A. Double the rate of the neuromuscular blocker every 5 minutes as needed until the patient stops moving.
   B. Increase the propofol infusion rate as needed to achieve sedation goals.
   C. Initiate a dexmedetomidine infusion.
   D. Check the TOF.

11. After that event, the patient did poorly the rest of the night. The patient was initiated on a norepinephrine infusion at 0.02 mcg/kg/minute to maintain an adequate blood pressure. Other medications initiated overnight included piperacillin/tazobactam, vancomycin, and gentamicin. By morning, her SCr has increased to 2.8 mg/dL, and the night shift nurse reports that the patient has had 0/4 twitches on TOF for the past 8 hours. Pertinent electrolyte values include K^+ 4.9 mEq/L, calcium 9 mg/dL, and magnesium 2 mg/dL. What is most likely to potentiate the effects of cisatracurium?
   A. Piperacillin/tazobactam.
   B. Gentamicin.
   C. Norepinephrine.
   D. K value of 4.9 mEq/L.

VII. GLUCOSE CONTROL

A. History of blood glucose control
   1. 2001: Study by van den Berghe et al. of surgical ICU patients showed a significant morbidity and mortality benefit of maintaining blood glucose at 80–110 mg/dL, despite the increased risk of hypoglycemia at 5.1% versus 0.8%.
   2. 2006: Study by van den Berghe et al. of primarily medical ICU patients showed no mortality benefit associated with maintaining blood glucose in the range of 80–110 mg/dL in the entire study population. The study showed a reduction in ventilator time, length of stay, and mortality in patients with an ICU length of stay of 3 days or more. The incidence of hypoglycemia (18%) was higher than previously reported.
   3. Subsequent investigations of tight glycemic control (80–110 mg/dL) never replicated the mortality benefit seen in the 2001 study. Studies showed much higher rates of hypoglycemia with tight glycemic control.
   4. 2009: Results of a large, international, randomized study (NICE-SUGAR) involving more than 6000 critically ill medical and surgical patients showed higher mortality and higher risk of hypoglycemia in patients receiving intensive blood glucose control (goal glucose 81–108 mg/dL) compared with patients having a goal of 180 mg/dL or less (mean blood glucose 142 mg/dL).
   5. The 2012 Society of Critical Care Medicine guidelines for using an insulin infusion to manage hyperglycemia in general critically ill patients suggest using a blood glucose of 150 mg/dL or higher as a trigger for insulin therapy, adjusted to keep blood glucose less than 150 mg/dL, and maintaining values less than 180 mg/dL using an insulin protocol that achieves a low rate of hypoglycemia (blood glucose 70 mg/dL or less).
   6. The 2016 SSC guidelines recommend a protocolized approach to insulin therapy, initiating insulin when two consecutive blood glucose readings are greater than 180 mg/dL. The target blood glucose concentration is 180 mg/dL or less for patients with sepsis.

B. Treatment strategies to achieve glycemic control in critically ill patients
   1. For a continuous insulin infusion approach, use a validated dosing protocol that considers blood glucose concentration, rate of change, and insulin infusion rate.
   2. Intravenous insulin is preferred for patients with type 1 diabetes, patients with hyperglycemia who are hemodynamically unstable, and patients in whom long-acting basal insulin should not be initiated because of changing clinical status. Once patients are in stable condition, they can be considered for transitioning to a protocol-driven subcutaneous insulin regimen.
   3. Regularly scheduled subcutaneous administration of basal or rapid-acting insulin can prevent hyperglycemia in clinically stable patients who do not need an intravenous infusion of insulin. The use of subcutaneous insulin is not recommended in patients taking vasopressors, patients with significant peripheral edema, or patients for whom rapid correction of blood glucose is warranted.
   4. Subcutaneous sliding-scale or correctional insulin should not be the sole method of glucose control in critically ill patients. A sliding-scale or correctional insulin regimen can be used in conjunction with the regularly scheduled subcutaneous doses; however, the baseline of insulin administered should be adjusted daily to prevent hyperglycemia and the need for additional doses of insulin.

C. Monitoring blood glucose
   1. For a continuous insulin infusion approach, monitoring of blood glucose every 1–2 hours is typically needed to provide safe and effective therapy.
   2. Interpret point-of-care testing of capillary blood with caution because it can overestimate plasma glucose values. Overestimation of blood glucose is more common in patients with anemia, hypotension, or hypoperfusion. It is also more common when blood glucose is in the hypoglycemic or hyperglycemic range.

3. Arterial or venous whole blood sampling is recommended instead of fingerstick capillary blood glucose testing in patients with shock or severe peripheral edema and for patients on a prolonged insulin infusion.

VIII. PREVENTING STRESS ULCERS

A. Mucosal bleeding in critically ill adults
   1. The incidence of stress-related mucosal bleeding in critically ill adults is estimated to be 2.5%.
   2. Signs and symptoms of stress ulcers include hematemesis, gross blood in gastric tube aspirates, coffee ground emesis or aspiration from gastric tube, and melena. Clinically significant stress ulcers are defined as those that cause hemodynamic compromise or necessitate blood transfusion.

B. Prophylactic therapy for stress ulcers
   1. Prophylactic medications are recommended for any one of the following major risk factors:
      a. Respiratory failure necessitating mechanical ventilation (for more than 48 hours)
      b. Coagulopathy, defined as platelet count less than 50,000 cells/mm^3, INR greater than 1.5, or activated partial thromboplastin time greater than twofold the control value. (Note: Prophylactic or treatment doses of anticoagulants do not constitute coagulopathy.)
   2. Prophylactic medications or continuing home acid suppressive regimens are also recommended for any patient with a history of gastrointestinal (GI) ulceration or bleeding within 1 year before ICU admission.
   3. Prophylactic medications are recommended for patients with two or more of the following risk factors (although data on this approach are lacking):
      a. Head or spinal cord injury
      b. Severe burn (more than 35% of body surface area)
      c. Hypoperfusion
      d. Acute organ dysfunction
      e. High doses of corticosteroids (more than 250 mg/day of hydrocortisone or equivalent)
      f. Liver failure with associated coagulopathy
      g. Transplantation
      h. Acute kidney injury
      i. Major surgery
      j. Multiple trauma

C. Strategies for stress ulcer prophylaxis (see Table 17 for specific medications)
   1. Efficacy of intravenous histamine-2 (H_2)-blockers in preventing stress-related upper GI bleeding has been shown in several clinical trials. These blockers are commonly administered enterally when possible because of excellent bioavailability; however, evidence of efficacy is primarily with the intravenous administration of H_2-blockers.
   2. Proton pump inhibitors (PPIs) also prevent stress-related mucosal bleeding and are commonly administered enterally, when possible, given their excellent bioavailability.
   3. Recent data analyses assessing PPIs versus placebo found no difference in mortality or clinically important events, which were a composite of clinically important GI bleeding, pneumonia, *C. difficile* infection, or myocardial ischemia. However, of note are the limited therapy duration (median of 4 days) and higher rate of GI bleeding in the placebo group (4.2% vs. 2.5%). Another large study comparing PPIs with H_2-blockers found no difference in mortality, but a lower incidence of clinically important GI bleeds with PPIs (1.3% vs. 1.8%; RR 0.73 [95% CI, 0.52–0.92]). However, 20.1% of patients randomized to H_2-blockers received PPIs, making it difficult to draw definitive conclusions and apply them to clinical practice (JAMA 2020;323:616-26).

4. Regardless of the drug choice or route, it is important to discontinue therapy when risk factors are no longer present to avoid unnecessary drug interactions, adverse effects (e.g., pneumonia), and increased costs. This step is easily overlooked, with the result that patients are discharged from hospitals and then continue to take acid-suppressive therapy with no indication.
5. Recent studies suggest enteral nutrition may have protective effects against GI bleeding. Pharmacologic prophylaxis may not provide additional benefit to EN, but may increase risk for adverse effects such as pneumonia. Additional studies are needed to confirm these outcomes.
6. Not recommended for prevention
    a. Antacids are not used to prevent stress ulcers.
    b. Sucralfate is inferior to H_2-blockers and is therefore not recommended for preventing stress ulcers. In addition, it can cause obstruction of enteral feeding tubes and aluminum toxicity in patients with renal failure.
    c. Safety: The benefits of preventing stress ulcers by increasing the stomach pH must be weighed against an increased risk of infection, including *C. difficile,* hospital-acquired pneumonia, and community-acquired pneumonia (for patients discharged with a PPI).

Table 17. Medications for Stress Ulcer Prophylaxis

Class	Examples and Dosing	Adverse Effects	Notes
H_2-receptor blockers	Ranitidine 150 mg PO every 12 hr or 50 mg IV every 8 hr Famotidine 20 mg IV or PO every 12 hr Nizatidine 150 mg PO every 12 hr Cimetidine 300 mg PO or IV every 6 hr or continuous infusion 37.5–50 mg/hr	Mental status changes, thrombocytopenia (cimetidine)	Excellent bioavailability Low cost Potential for reduced efficacy over time (tachyphylaxis) Dose adjustment for renal dysfunction Low risk of nosocomial pneumonia Cimetidine not routinely used because of drug interactions (strong P450 inhibitor) and adverse effects
Proton pump inhibitors	Omeprazole 20 mg PO daily Powder for oral suspension available Esomeprazole 20–40 mg PO or IV daily Lansoprazole 30 mg PO or IV daily Delayed-release orally disintegrating tablets and oral suspension available Pantoprazole 40 mg PO or IV daily granules available for oral or tube administration	Headache, diarrhea, constipation, abdominal pain, nausea	Solutions of certain PPIs may be compounded; refer to individual package inserts for instructions No adjustment needed for renal or liver dysfunction Higher cost than H_2-blockers Administration problems may occur when given by feeding tubes Risk of ventilator-associated pneumonia increased Risk of *C. difficile* infection (nosocomial or community acquired)

H_2 = histamine-2; IV = intravenous; PO = orally; PPI = proton pump inhibitor.

Patient Case

Questions 12 and 13 pertain to the following case.

A 73-year-old woman (weight 84 kg) is admitted to the ICU after a pneumonectomy. Her blood pressure is 104/65 mm Hg, heart rate is 88 beats/minute, and Sao_2 values are 98% on 40% Fio_2 and PEEP 5 cm H_2O; her Glasgow Coma Scale score is 11. Her other laboratory values are normal. Her medications include simvastatin 20 mg every night, aspirin 81 mg/ day, metoprolol 25 mg twice daily, heparin 5000 units subcutaneously every 8 hours, and 0.9% sodium chloride intravenously at 75 mL/hour.

12. The surgeon would like to initiate SUP. Which is the best recommendation for this patient?
    A. Administer famotidine 20 mg per tube every 12 hours.
    B. Administer magnesium hydroxide 30 mL per tube four times daily.
    C. Administer sucralfate 1 g per tube four times daily.
    D. SUP is not indicated.

13. One week later, the patient is extubated but still in the ICU. Her Glasgow Coma Scale score is 15, blood pressure is 112/70 mm Hg, and heart rate is 75 beats/minute, but her appetite is poor. Which statement is most appropriate regarding SUP for this patient?
    A. SUP should continue until the patient is discharged from the ICU.
    B. SUP should be discontinued now.
    C. Continue SUP until patient is eating.
    D. SUP should be discontinued at hospital discharge.

IX. PHARMACOLOGIC THERAPY FOR PREVENTING VENOUS THROMBOEMBOLISM

A. General overview: VTE is a common complication of critical illness, with an incidence of deep vein thrombosis of 8%–40% and pulmonary embolism of up to 12%.

B. Risk factors for VTE
    1. Critically ill patients are usually at high risk of VTE.
    2. Additional risk factors include surgery, major trauma, lower extremity injury, immobility, malignancy, sepsis, heart failure, respiratory failure, venous compression, previous VTE, increasing age, pregnancy, erythropoiesis-stimulating agents, obesity, and central venous catheterization.

C. Nonpharmacologic prevention of VTE
    1. Early mobility is the ideal nonpharmacologic therapy.
    2. Mechanical prophylaxis with intermittent pneumatic compression or graduated compression stockings is recommended for medical patients at risk of VTE who have a contraindication to pharmacologic anticoagulation (e.g., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage).
    3. Mechanical prophylaxis should be used in combination with pharmacologic treatment.

D. Recommendations for critically ill patients
   1. American College of Chest Physicians, ninth edition
      a. Recommends low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin over no prophylaxis
      b. For patients who are bleeding or at high risk for major bleeding, the guidelines recommend mechanical thromboprophylaxis and institution of pharmacologic prophylaxis when the bleeding risk decreases.
      c. The guidelines provide separate postoperative recommendations. A detailed assessment is beyond the scope of this text, and readers are encouraged to see the guideline for more information.
   2. SSC also provides recommendations that are identical to those above.

E. Pharmacologic prophylaxis (see Table 18 for dosage)
   1. Unfractionated heparin
      a. Low cost
      b. Twice- versus three-times daily administration: Two meta-analyses have been completed on the subject. The first, in 2007, concluded that there was no difference in efficacy, but three-times daily administration was associated with a slightly higher risk of bleeding. The second, in 2011, found no difference in efficacy or safety with either regimen.
      c. Risk of heparin-induced thrombocytopenia (HIT) lower than that of full anticoagulation doses
   2. LMWHs
      a. All considered therapeutically equivalent
      b. Dalteparin is renally eliminated but can be considered in patients with creatinine clearance (CrCl) less than 30 mL/minute/1.73 m^2 because of its low accumulation.
      c. Low risk of HIT
      d. In the largest trial of VTE prevention in critical care patients, dalteparin 5000 units subcutaneously once daily provided better protection against pulmonary embolism, similar protection against proximal deep venous thrombosis with no difference in bleeding, and less HIT than unfractionated heparin 5000 units twice daily.
   3. Fondaparinux
      a. Can be safe in patients with a history of HIT
      b. Data on reversal of fondaparinux are lacking
      c. Contraindicated for CrCl less than 30 mL/minute/1.73 m^2
      d. Limited data in critically ill patients
   4. Direct oral anticoagulants
      a. Rivaroxaban was evaluated against enoxaparin in a study of acutely ill medical patients needing hospitalization. Although rivaroxaban was as efficacious as enoxaparin at study day 10, there was an excess risk of bleeding in the rivaroxaban group. Patients with cardiogenic or septic shock with the need for vasopressors were excluded. Rivaroxaban is renally eliminated and is not recommended in patients with renal insufficiency.
      b. Apixaban was evaluated against enoxaparin in a study of acutely ill medical patients needing hospitalization. There was no difference in rates of VTE, but a higher bleeding rate with apixaban. Patients with septic shock were also excluded from this trial.
      c. Betrixaban was also evaluated against enoxaparin in a study of acutely ill medical patients needing hospitalization. Betrixaban significantly reduced VTE events with no significant increases in major bleeding compared with enoxaparin for 10 days.
      d. Compared with heparins, there is limited experience in reversal of Factor Xa inhibitors in clinical practice.
      e. Rivaroxaban and betrixaban are the only direct-acting anticoagulants (DOACs) FDA-approved for VTE prophylaxis in medically ill patients. However, the safety and efficacy of both agents in critically ill patients are still unclear.

F. Special populations
   1. Impaired kidney function
      a. If estimated CrCl is less than 30 mL/minute/1.73 m^2, LMWH dose reduction is usually necessary. If CrCl is less than 20 mL/minute/1.73 m^2 or the patient requires dialysis, dosing information is limited for LMWH; anti-Xa monitoring might not be reliable in patients undergoing dialysis.
      b. Alternatively, if estimated CrCl is less than 30 mL/minute/1.73 m^2, dalteparin can be used because it has minimal renal metabolism.
      c. Fondaparinux is contraindicated in patients with an estimated CrCl less than 30 mL/minute 1.73 m^2.
      d. Low-dose unfractionated heparin is minimally renally eliminated and is safe to use in patients with reduced kidney function.
   2. Overweight or underweight adults: For patients with obesity, some experts recommend increasing unfractionated heparin dose to 7500 units and LMWH prophylaxis doses by 30%–100% if body mass index (BMI) is greater than 40 kg/m^2; a peak (4 hours postdose) anti-Xa of 0.2–0.4 IU/mL is recommended. Note that these recommendations have not been validated in controlled trials and are considered expert opinion only (see Ann Pharmacother 2009;43:1064-83).
   3. Patients admitted with major traumatic injuries: Enoxaparin 30 mg every 12 hours is more effective than other regimens.

G. Antithrombotic therapy and regional anesthesia
   1. Critically ill patients often have their spinal meninges accessed for either therapeutic (epidural anesthesia, lumbar drains) or diagnostic (lumbar puncture) purposes.
   2. The combination of antithrombotic medications with these techniques is associated with an elevated risk of spinal or epidural hematoma, which can lead to ischemia and paralysis.
   3. The American Society of Regional Anesthesia and Pain Medicine published guidelines on regional anesthesia in patients receiving antithrombotic or thrombolytic therapy.
      a. There is no contraindication to low-dose unfractionated heparin at daily doses of less than 10,000 units (i.e., 5000 units every 12 hours). It is unknown whether subcutaneous heparin at doses greater than 10,000 units daily (i.e., 5000 units every 8 hours) carries a higher risk of complication than lower doses do. If patients receive subcutaneous heparin at doses greater than 10,000 units daily, enhanced monitoring for neurologic deficits should occur.
      b. For patients receiving LMWH, needle placement should occur 10–12 hours after the last LMWH dose (longer in patients with renal disease).
      c. Indwelling catheters should be removed before initiation of twice-daily LMWH postoperatively, but can be maintained for patients on once-daily regimens.
         i. The first dose of LMWH should be at least 2 hours after catheter removal.
         ii. Catheter removal should be at least 10–12 hours after the last LMWH dose (longer in patients with renal disease).
      d. Because of a lack of data and early clinical trial data, the use of fondaparinux should be avoided.
      e. Because of various DOAC regimens with differences in half-life and elimination, check for specific recommendations regarding regional analgesia.

H. Prevention of VTE: Pharmacologic options in critically ill patients

Table 18. Prevention of Venous Thromboembolism: Pharmacologic Options

Medication	Mechanism	Dosing[a]	Adjustment for Renal Dysfunction
Unfractionated heparin	Factor Xa and indirect thrombin inhibition	5000 units SC two or three times daily	None
Low-molecular-weight heparin	Factor Xa inhibition and some indirect thrombin inhibition	Enoxaparin 40 mg SC daily Dalteparin 5000 units SC daily	CrCl < 30 mL/min/1.73 m^2: enoxaparin 30 mg SC daily
Fondaparinux	Factor Xa inhibition	2.5 mg SC daily	Contraindicated for CrCl < 30 mL/min/1.73 m^2

[a]Patients within normal body mass index (BMI) range.
SC = subcutaneously.

X. PREVENTING VENTILATOR-ASSOCIATED PNEUMONIA

A. The Institute for Healthcare Improvement has developed a ventilator bundle with the following elements that directly target ventilator-associated pneumonia and complications arising from it.
   1. Head of the bed elevation: Maintain the head of the bed elevated (about 30–45 degrees).
   2. Daily sedation interruptions and assessment of readiness to extubate
   3. Stress ulcer prophylaxis
   4. VTE prophylaxis
   5. Daily oral care with chlorhexidine (0.12% oral rinse)

B. Additional methods
   1. Selective decontamination of the digestive tract
      a. It is a short course of antimicrobial therapy aimed at eradicating potential pathogens to minimize ICU-acquired infections.
      b. Selective decontamination is still not routinely performed and is not supported by the guidelines because of the risk of promoting antimicrobial resistance.
   2. Endotracheal tubes coated in an antimicrobial (silver) reduce infection but are cost prohibitive in many centers.

XI. NUTRITION SUPPORT IN CRITICALLY ILL PATIENTS

A. General overview
   1. Many critically ill patients have increased caloric and protein needs, and caloric deficit in these patients leads to excess morbidity (length of stay, infection) and mortality.
   2. Skeletal muscle wasting and weakness occurring during critical illness may lead to prolonged mechanical ventilation and rehabilitation.
   3. Ideally, nutrition should be provided within 24–48 hours of admission to the ICU.
   4. Route of delivery (EN vs. PN)
      a. In general, EN is preferred to PN in patients with a functional GI tract and who are not malnourished.
      b. American and Canadian guidelines allow hypocaloric feeding during the first 7 days in previously well-nourished patients before consideration of PN.
      c. The SSC guidelines recommend intravenous glucose and EN rather than total PN alone or PN in conjunction with EN in the first 7 days after a diagnosis of sepsis or septic shock.
      d. PN is recommended for patients with extensive small bowel resection, chronic malabsorption, high-output enterocutaneous fistulas, severe malnutrition at baseline, suspected or confirmed GI ischemia, mechanical bowel obstruction, or persistent, severe hemodynamic instability.

B. Estimating nutrition needs
   1. Traditional biomarkers of nutrition (albumin, prealbumin, nitrogen balance) are not well validated in critically ill patients.
   2. Indirect calorimetry and predictive equations can be used to determine energy needs in critically ill patients.
      a. Indirect calorimetry measures the metabolic rate, but it requires special equipment and trained staff and is subject to inaccuracies in some patient populations. Indirect calorimetry also provides a respiratory quotient (RQ), indicating substrate metabolism and allowing modification of macronutrient delivery (e.g., carbohydrates, fats, protein).
         i. RQ 1.0–1.3: Lipogenesis (overfeeding), hyperventilation, or system "leak"
         ii. RQ 0.9–1.0: Primary carbohydrate oxidation, metabolic acidosis
         iii. RQ 0.82–0.85: Normal, "mixed" substrate oxidation
         iv. RQ 0.80: Primary protein oxidation
         v. RQ 0.70: Primary fat oxidation, systemic inflammatory response syndrome, metabolic alkalosis, or ethanol oxidation
         vi. RQ less than 0.67 or greater than 1.3: Outside range; question test validity
      b. Several predictive equations for determining caloric goals have been used (e.g., Harris-Benedict, Penn State and modified Penn State, Ireton-Jones, Mifflin, and Swinamer equations). Each comes with variable accuracy rates compared with indirect calorimetry. A single equation has not been shown to be best across various ICU populations.
      c. Some guidelines recommend a 25-kcal/kg actual body weight target, but this approach may be too simplistic for most critically ill patients.
      d. See the references for a review of the usefulness of predictive equations in critically ill patients.
   3. Hypocaloric feeding
      a. The SSC recommends avoiding mandatory full caloric feeding in the first week, but suggests low-dose feeding (i.e., up to 500 kcal per day), advancing only as tolerated.
      b. One study showed that intentional underfeeding (60%–70% of target) of critically ill patients while providing 90%–100% of protein needs showed a significant reduction in hospital mortality.
      c. It is recommended that patients with obesity (BMI greater than 30 kg/m^2) can be fed at 60%–70% of target energy requirements or 11–14 kcal/kg actual body weight per day. Protein should be delivered in the range of 2–2.5 g/kg ideal body weight per day.
   4. Protein needs
      a. The stress response in critical illness increases gluconeogenesis, which cannot be fully suppressed by exogenous glucose.
      b. Protein intake of 1.2–2 g/kg of actual body weight is recommended in most critically ill patients.
         i. Patients on continuous renal replacement therapy may need up to 2.5 g/kg per day.
         ii. Protein restriction is generally not recommended for patients with acute kidney injury who are not receiving renal replacement.
         iii. Patients with extensive burn injury may need up to 3 g/kg per day.

C. Enteral nutrition
   1. It is important to recognize that the prescribed dose of EN is often not delivered to patients because of interruptions, intolerance, or many other reasons. Use of an EN protocol with guidance on initiation, advancement, and interruptions is essential.
   2. "Trophic" feeding, or low-dose enteral feeding with the intent of maintaining GI tract function, is commonly used despite limited evidence.
   3. EN can be delivered safely to patients receiving low-dose vasopressors.

4. Gastric versus small bowel (postpyloric) feeding delivery
    a. Delivery of EN directly into the small bowel may be associated with a reduction in pneumonia.
    b. In units where small bowel access is readily available, routine use of small bowel feeding is recommended.
    c. If small bowel access is not readily available, then small bowel feedings should be considered only for patients at high risk of intolerance to EN (on inotropes, continuous infusion of sedatives, or paralytic agents, or patients with high nasogastric drainage) or at high risk for regurgitation and aspiration (nursed in supine position) or who have repeatedly demonstrated intolerance of gastric feeds.
5. Gastric residual volumes
    a. There are no data indicating that interruption of gastric feeding for a specific residual volume prevents morbidity (aspiration pneumonia) in critically ill patients. The guidelines do not recommend routine checking of residual volume to assess aspiration risk. However, residuals may still be checked if there is concern for tolerance or to assess gastric motility, especially in patients with recent bowel surgery.
    b. A residual volume of 250–500 mL is recommended as a point where intervention should occur. Prokinetic agents such as metoclopramide and erythromycin may be given to decrease residuals and enhance gastrointestinal motility.

D. Parenteral nutrition
1. Parenteral nutrition should be administered via the central vein whenever possible. Peripheral administration is possible, but it must be dilute and can cause problems with the volume of the solution.
2. Intravenous catheters intended for PN should not be used for any other purpose.
3. Blood glucose measurements should be taken at least every 4–6 hours for patients receiving PN during initiation and changes in carbohydrate content.

E. Supplemental antioxidants and immunomodulation: Supplemental antioxidants and immunomodulating micronutrients (vitamin E, selenium, fish oils, arginine, glutamine, zinc) are not recommended for general critically ill patients.

F. In addition to the SSC, the American Society of Parenteral and Enteral Nutrition publishes guidelines in conjunction with the Society of Critical Care Medicine (Crit Care Med 2016;44:390-438).

G. Further guidance: See “Fluids, Electrolytes, and Nutrition” chapter.

Patient Case

Questions 14 and 15 pertain to the following case.

A 75-year-old woman (height 65 inches [165 cm], weight 68 kg) who is intubated needs mechanical ventilation for an acute exacerbation of chronic obstructive pulmonary disease. She has a medical history of heart failure and hypertension. Her laboratory values are normal except for a creatinine level of 1.9 mg/dL.

14. Which is the most appropriate recommendation to prevent VTE in this patient?
    A. Initiate intermittent pneumatic compression.
    B. Administer fondaparinux 2.5 mg subcutaneously once daily.
    C. Administer enoxaparin 30 mg subcutaneously twice daily.
    D. Administer heparin 5000 units subcutaneously three times daily.

15. Three days later, the patient continues to need mechanical ventilation. Enteral nutrition has been initiated through her nasogastric feeding tube and has gradually been increased to her goal of 45 mL/hour. Over the past day, her gastric residuals are consistently 300–350 mL. Which statement is most appropriate to optimize this patient's nutrition support?
    A. Change to PN.
    B. Add metoclopramide 5 mg intravenously every 6 hours.
    C. Change feeds to a more concentrated formula.
    D. Decrease tube feeds to 10 mL/hour.

XII. INTRACRANIAL HEMORRHAGE

A. General overview
    1. Intracranial hemorrhage (ICH) is a broad term that encompasses many clinical scenarios. Goals of care are to minimize hemorrhage expansion and to treat associated organ dysfunction, thereby decreasing mortality and improving quality of life.
    2. ICH is classified by the anatomic location of the bleeding.
        a. Intraparenchymal hemorrhage (IPH): Nontraumatic bleeding into the brain parenchyma
        b. Subarachnoid hemorrhage (SAH): Bleeding into the space between the pia and arachnoid membranes that can be caused by rupture of a cerebral aneurysm, bleeding from arteriovenous malformations, tumors, amyloid angiopathy, or vasculopathy. Patients may present early on with the classic "worst headache of my life."
        c. Subdural hematoma (SDH) – Bleeding between the dura and arachnoid space
        d. Epidural hematoma (EDH) – Bleeding between the dura and the bone
    3. Subdural and epidural hematomas are usually caused by traumatic injury.
    4. Severity of ICH and resulting neurologic injury guide diagnostic tests, treatment, and prognosis. Commonly used scales include the Glasgow Coma Scale (GCS; Table 19) to assess the level of consciousness and the National Institutes of Health Stroke Scale. Disease-specific scales are also used for SAH and IPH. The Hunt and Hess scale is a qualitative scale that rates patients with SAH from 1 (no symptoms) to 5 (deeply comatose). The Fisher scale rates the amount of blood present in patients with SAH from 1 (no blood visualized) to 4 (diffuse SAH, ICH, or intraventricular hemorrhage present). Because the etiologies of IPH and SAH are different, the ICH score is used for IPH. The ICH score is a composite score consisting of hemorrhage size, age, site of hemorrhage, and GCS scores and ranges from 0 (best) to 6 (worst).

Table 19. Glasgow Coma Scale

Axes	Score
Eye Opening	
Does not open eyes	1
Opens eyes in response to painful stimuli	2
Opens eyes in response to voice	3
Opens eyes spontaneously	4
Motor Response	
Makes no movements	1
Extension to painful stimuli	2
Abnormal flexion to painful stimuli	3
Flexion or withdrawal to painful stimuli	4
Localizes painful stimuli	5
Obeys commands	6
Verbal Response	
Makes no sounds	1
Incomprehensible sounds	2
Utters appropriate words	3
Confused, disoriented	4
Oriented, converses normally	5

B. Risk factors
   1. Hypertension is the most common risk factor.
   2. Use of fibrinolytic (e.g., alteplase), anticoagulant, and antiplatelet medications
   3. Amyloid angiopathy
   4. Intracranial aneurysm
      a. Rupture may be spontaneous or may result from exertion or hypertension.
      b. Risk factors for rupture include tobacco use, hypertension, cocaine use, a history of SAH, familial history of SAH, large aneurysm size, female sex, connective tissue disease, and older age.
   5. Liver failure–induced coagulopathy
   6. Mycotic aneurysms

C. Management
   1. Blood pressure control
      a. Acute hypertension should be controlled after the diagnosis of SAH. The goal blood pressure has not been definitively established. AHA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage recommend balancing the risk of stroke, rebleeding because of hypertension, and maintenance of cerebral perfusion pressure in determining a patient's goal blood pressure. They further state that a goal systolic blood pressure less than 160 mm Hg is reasonable.
      b. Elevated blood pressure is associated with greater hematoma expansion, neurologic deterioration, and death after ICH. The AHA/ASA guidelines for managing spontaneous intracerebral hemorrhage recommend acute lowering of SBP to 140 mm Hg for patients with SBP of 150–220 mm Hg and no contraindication to acute blood pressure treatment. For patients with SBP greater than 220 mm Hg, it may be reasonable to consider aggressive blood pressure reduction with a continuous intravenous agent. INTERACT2 is the largest randomized trial assessing intensive treatment (SBP less than 140 mm Hg) versus guideline-recommended treatment (SBP less than 180 mm Hg). There was no difference in death or disability at 90 days, but functional outcomes were improved with intensive blood pressure control.

   c. Blood pressure should be controlled with an intravenous, titratable agent such as nicardipine or clevidipine. Comparisons of agents and clinical outcomes are lacking. Details on antihypertensive agents are available in the "Acute Care in Cardiology" chapter.
2. Antifibrinolytic therapy
   a. For patients who will have a delay in surgical intervention after an aneurysmal SAH, short-term (less than 72 hours or until angiography) treatment with tranexamic acid or aminocaproic acid (preferred) is reasonable.
   b. The TICH-2 trial evaluating tranexamic acid in acute ICH found no difference in functional status or mortality at 90 days. Because of a lack of benefit, tranexamic acid should not routinely be given in this patient population. Tranexamic acid is administered as a 1 g load followed by 1 g infused over eight hours.
   c. Many different dosing protocols exist for aminocaproic acid and tranexamic acid. Typically, aminocaproic acid is administered as a 4- to 5-g load followed by 1 g/hour.
   d. Patients who receive antifibrinolytic therapy should be monitored for the development of a VTE.
3. Coagulation factors: In a study of ICH not caused by anticoagulant therapy, recombinant activated factor VII decreased the size of ICH but did not improve outcomes.
4. Seizure prophylaxis in aneurysmal SAH
   a. The incidence of seizures after SAH may reach 20%, seen mainly at the time of rupture, with the incidence decreasing after treatment. The use of antiepileptic drugs is controversial and may stem from earlier studies that used primarily phenytoin for prophylaxis. Current guidelines state that prophylaxis can be considered in the immediate posthemorrhage period.
   b. Phenytoin is subject to drug interactions, notably with nimodipine (decreasing nimodipine serum concentrations). Both the AHA and the Neurocritical Care Society guidelines recommend against the use of phenytoin because of adverse outcomes.
   c. Levetiracetam is generally considered a safer antiepileptic drug, but data supporting its use are limited.
5. Seizure prophylaxis in ICH: Compared with SAH, the incidence of seizures is estimated to be the same or slightly higher; however, seizures can present at the onset or occur late in therapy because of scarring. The current AHA guidelines on ICH recommend against prophylactic anticonvulsants; however, this may be because of early studies that used primarily phenytoin.
6. Vasospasm
   a. Vasospasm is the acute narrowing of the cerebral arteries after aneurysmal SAH. It is most common during the first 7–10 days after aneurysm rupture and the risk typically resolves after 21 days. Untreated, vasospasm leads to delayed cerebral ischemia, a major cause of death and disability.
   b. Oral nimodipine 60 mg every 4 hours for 21 days should be administered in all patients with aneurysmal SAH. Although this agent does not decrease the incidence of vasospasm it has been shown to improve outcomes. For patients who are unable to tolerate 60 mg every 4 hours because of hypotension, 30 mg every 2 hours is also an option.
   c. Triple-H therapy (hypertension, hypervolemia, hemodilution) is no longer recommended. Euvolemia should be maintained in all patients. Large volumes of hypotonic fluids should be avoided.
7. Microsurgical clip obliteration by craniotomy and endovascular coiling are both interventions for aneurysmal SAH that should be performed as early as possible. Determination regarding which procedure yields better outcomes is ongoing. Advancements in both approaches have improved the rate of survival and lowered the rate of disability.

REFERENCES

Acid Base

1. Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders. Part I. N Engl J Med 1998;338:26-34.
2. Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders. Part II. N Engl J Med 1998;338:107-11.
3. Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. N Engl J Med 2014;371:1434-45.
4. Haber RJ. A practical approach to acid-base disorders. West J Med 1991;155:146-51.

Shock and Sepsis

1. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840-51.
2. ARISE Investigators, ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506.
3. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
4. Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock. JAMA 2020;323:423-31.
5. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Crit Care Med 2018;46:997-1000.
6. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock. Chest 2017;15:1229-38.
7. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. Intensive Care Med 2016;43:304-77.
8. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
9. Russell JA. Management of sepsis. N Engl J Med 2006;355:1699-713.
10. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
11. Surviving Sepsis Campaign Bundles. Available at www.survivingsepsis.org/Bundles/Pages/default.aspx. Accessed October 2, 2017.

Steroids

1. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit Care Med 2017;45:2078-88.
2. Annane D, Renault A, Brun-Buisson B, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809-18.
3. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-70.
4. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36:1937-49.
5. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-4.
6. Sprung CL, Brezis M, Goodman S, et al. Corticosteroid therapy for patients in septic shock: some progress in a difficult decision. Crit Care Med 2011;39:571-4.
7. Venkatatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797-808.

Volume Replacement and Vasopressors

1. Chew MS, Åneman A. Haemodynamic monitoring using arterial waveform analysis. Curr Opin Crit Care 2013;19:234-41.

2. DeBacker D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
3. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247-56.
4. Hammond DA, Lam SW, Rech MA, et al. Balanced crystalloids versus saline in critically ill adults: a systematic review and meta-analysis. Ann Pharmacother 2020;54:5-13.
5. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;337:419-30.
6. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877-87.
7. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA 2015;314:1701-10.
8. Yunos N, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308:1566-72.
9. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 2013;309:678-88.

Cardiac Arrest

1. American Heart Association (AHA). American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S315-67.
2. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S465-82.
3. Johnson NJ, Danielson KR, Counts CR. Targeted temperature management at 33 versus 36 degrees: a retrospective cohort study. Crit Care Med 2020;48:362-9.
4. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197-206.
5. Nunnally ME, Jaeschke R, Bellingan GJ, et al. Targeted temperature management in critical care: a report and recommendations from five professional societies. Crit Care Med 2011;39:1113-25.
6. Park SM, Mangat HS, Berger K, Rosengart AJ. Efficacy spectrum of antishivering medications: meta-analysis of randomized controlled trials. Crit Care Med 2012;40:3070-82.
7. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007;35:2196-204.

Sedation

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
2. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825-73.
3. Jakob SM, Ruokonen E, Grounds RM, et al; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.
4. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7.
5. Mazzeffi M, Johnson K, Paciullo CA. Ketamine in adult cardiac surgery and the cardiac surgery intensive care unit: an evidence-based clinical review. Ann Card Anaesth 2015;18:202-9.
6. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92.

7. Pun B, Dunn J. The sedation of critically ill adults: part 1. Assessment. Am J Nurs 2007;107:40-8.
8. Sessler CN, Varney K. Patient-focused sedation and analgesia in the ICU. Chest 2008;133:552-65.

Delirium

1. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-62.
2. Gilchrist NA, Asoh I, Greenberg B. Atypical antipsychotics for the treatment of ICU delirium. J Intensive Care Med 2012;27:354-61.
3. ICU Delirium and Cognitive Impairment Study Group. Brain dysfunction in critically ill patients. Vanderbilt Medical Center. Available at www.icudelirium.org/delirium. Accessed October 2 2017.

Neuromuscular Blockade

1. Baumann MH, McAlpin BW, Brown K, et al. A prospective randomized comparison of train-of-four monitoring and clinical assessment during continuous ICU cisatracurium paralysis. Chest 2004;126:1267-73.
2. Moss M, Huang DT, Brower RG, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380:1997-2008.
3. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2002;30:142-56.
4. Murray MJ, DeBlock H, Erstad B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2016;44:2079-03.
5. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.

Glucose Control

1. Jacobi J, Bircher N, Krinsley J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012;40:3251-76.
2. Kavanagh BP, McCowen KC. Glycemic control in the ICU. N Engl J Med 2010;363:2540-6.
3. NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.
4. Van den Berghe, G., Wilmer, A., Hermans, G., et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-61.
5. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.

Stress Ulcer Prophylaxis

1. Allen ME, Kopp BJ, Erstad BL. Stress ulcer prophylaxis in the postoperative period. Am J Health Syst Pharm 2004;61:588-96.
2. ASHP Commission on Therapeutics. ASHP therapeutic guidelines on stress ulcer prophylaxis. Am J Health Syst Pharm 1999;56:347-79.
3. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N Engl J Med 1998;338:791-7.
4. Herzig SJ, Howell MD, Ngo LH, et al. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 2009;301:2120-8.
5. Huang HB, Jiang W, Wang CY, et al. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. Crit Care 2018;22:20.
6. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med 2018;379:2199-208.
7. PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: the PEPTIC randomized clinical trial. JAMA 2020;323:616-26.
8. Sessler JM. Stress-related mucosal disease in the intensive care unit: an update on prophylaxis. AACN Adv Crit Care 2007;18:199-26.

9. Stevens AM, Thomas Z. The case against stress ulcer prophylaxis in 2007. Hosp Pharm 2007;42:995-1002.

Preventing VTE

1. Alhazzani W, Lim W, Jaeschke RZ, et al. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care Med 2013; 41:2088-98.
2. Cohen AT, Harrington RA, Goldhaber SZ, et al.; for the APEX Investigators. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med 2016;375:534-44.
3. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 2013;368:513-23.
4. Cook D, Meade M, Guyatt G, et al. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 2011;364:1305-14.
5. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients. Chest 2012;141(suppl 2):e227S-77S.
6. Guyatt GH, Akl EA, Crowther DD, et al. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl 2):7S-47S.
7. Nutescu EA. Assessing, preventing, and treating venous thromboembolism: evidence-based approaches. Am J Health Syst Pharm 2007;64 (suppl 7):5-13.
8. Phung OJ, Kahn SR, Cook DJ, et al. Dosing frequency of unfractionated heparin thromboprophylaxis. Chest 2011;140:374-81.

Prevention of Ventilator-Associated Pneumonia

1. IHI Ventilator Bundle. Available at www.ihi.org/resources/Pages/Changes/ImplementtheVentilatorBundle.aspx. Accessed October, 2, 2017.

Nutrition

1. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr 2011;93:569-77.
2. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.
3. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370:1227-36.
4. Dhaliwal R, Cahill N, Lemieux M, et al. The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. Nutr Clin Pract 2014;29: 29-43.
5. Dickerson RN, Boschert KJ, Kudsk KA, et al. Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition 2002;18:241-6.
6. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. Crit Care Med 2016;44:390-438.
7. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: executive summary. Crit Care Med 2009;37:1757-61.
8. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med 2016;44: 390-438.
9. Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. Respir Care 2009;54:509-21.
10. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009;361:1088-97.

Intracranial Hemorrhage

1. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355-65.
2. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. Stroke 2012:43;1711-37.

3. Diringer MN, Bleck TP, Hemphill JC, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care 2011;15: 211-40.
4. FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2008;358:2127-37.
5. Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:2032-60.
6. Lawton MT, Vates GE. Subarachnoid hemorrhage. N Engl J Med 2017;377:257-66.
7. Naidech AM. Intracranial hemorrhage. Am J Respir Crit Care Med 2011;184:998-1006.
8. Rowe SA, Goodwin H, Brophy GM, et al. Seizure prophylaxis in neurocritical care: evidence-based support. Pharmacotherapy 2014;34:396-409.
9. Sprigg N, Flaherty K, Appleton JP. Tranexamic acid for hyperacute primary intracerebral hemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet 2018;391:2107-15.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient's ABG is consistent with metabolic acidosis. The pH is less than 7.40, indicating primary acidosis (Answer C is incorrect). The HCO_3^- and $Paco_2$ are lower than normal, indicating this is metabolic in origin (Answer D is incorrect). In metabolic acidosis, the decrease in HCO_3^- is the primary disorder. When metabolic acidosis is present, the AG should be calculated to provide additional insight about the potential cause of the disorder. The AG is calculated by subtracting the sum of measured anions (Cl^- and HCO_3^-) from cations (Na^+). This patient's AG (8 mEq/L) is within the reference range of 6–12 mEq/L; therefore, it is called a normal AG metabolic acidosis or non-AG metabolic acidosis (Answer B is correct; Answer A is incorrect). *C. difficile*–induced diarrhea is the most likely cause of this patient's acid-base disorder.

2. Answer: D

In patients without chronic obstructive pulmonary disease, a $Paco_2$ greater than 50 mm Hg is usually an indication for mechanical ventilation, regardless of oxygenation status. Oxygen (Answer B) therapy alone is unlikely to correct this patient's cause of respiratory failure (i.e., hypoventilation). Similarly, his acid-base disturbance is consistent with a pure acute respiratory acidosis (elevated $Paco_2$, normal HCO_3-) and is therefore unlikely to respond to HCO_3- (Answer C). Acetazolamide (Answer A) is used for metabolic alkalosis. Given this patient's neurologic status and elevated $Paco_2$, he should be intubated and transferred to the ICU (Answer D is correct).

3. Answer: C

This patient's ABG is consistent with respiratory acidosis. The pH is below 7.40, indicating acidosis (Answer D is incorrect). The $Paco_2$ is higher than normal (about 40 mm Hg). In chronic respiratory acidosis, the kidneys conserve HCO_3- (a base) to maintain a normal pH. This patient's compensatory metabolic alkalosis is obvious, given that her serum HCO_3- is 28 mEq/L (which is about 4 mEq/L higher than normal). This patient's elevated HCO- concentration confirms the diagnosis of respiratory acidosis (because the HCO_3- would be less than 24 mEq/L if the acidemia were attributable to a metabolic cause) (Answer C is correct; Answers A and B are incorrect).

4. Answer: C

This patient's hemodynamic profile is most consistent with sepsis (i.e., high CI, low SVR). Her PCWP is consistent with an adequate volume challenge. Because she remains hypotensive despite receiving an adequate fluid load, norepinephrine (Answer C) should be initiated because it is the initial vasopressor of choice in septic shock. Dobutamine (Answer B) is an inotropic agent that increases CI, which is adequate in this patient. If the patient continues to be hypotensive despite adequate fluid resuscitation and use of norepinephrine, angiotensin II (Answer A) can be considered. Dopamine is an alternative to norepinephrine, but it is not preferred because it is associated with a higher incidence of arrhythmias than norepinephrine (Answer D is incorrect).

5. Answer: B

Calculating an infusion rate is an important role for the pharmacist in code situations. The infusion pump is set to run in milliliters per hour; therefore, the answer should always be in these units. To determine the rate (in milliliters per hour) needed to achieve a 0.05-mcg/kg/minute dose, use the following calculation: concentration of norepinephrine drip: 4 mg/250 mL = 0.016 mg/mL or 16 mcg/mL. Therefore, 75 kg × 0.05 mcg/kg/minute × 60 minutes/1 hour × 1 mL/16 mcg = 14.0625 mL/hour, which is then rounded to 14 mL/hour (Answer B is correct; Answers A, C, and D are incorrect).

6. Answer: B

The patient received adequate fluid resuscitation over several hours, and additional fluids are not needed at this time (Answer D is incorrect). Hydrocortisone is not necessary in this case because the patient is responding to fluid resuscitation and the infusion of norepinephrine, as evidenced by the increase in MAP from 44 mm Hg on arrival at the emergency department to 66 mm Hg after initial resuscitation (Answer A is incorrect). Changing to dopamine is not necessary at this time because the MAP is greater than 65 mm Hg, thus allowing global organ perfusion (Answer C is incorrect). In addition, there is no evidence that a low dose of dopamine will prevent acute kidney injury, and it increases the risk of arrhythmias compared with norepinephrine. The patient's heart rate increased significantly to 148 beats/minute while receiving norepinephrine.

Phenylephrine is an alternative to consider in patients with vasopressor-induced tachyarrhythmias (Answer B is correct).

7. Answer: A

During rewarming, patients can become hypoglycemic. Therefore, a reduction in the insulin infusion is likely, and blood glucose should be monitored more often (Answer A). Neuromuscular blockade assessment can include titrating to a TOF goal; however, a more applicable goal would be the absence of shivering in this patient when the paralytic is briefly interrupted. If the patient is not shivering, consideration should be given to discontinuing the paralytic. Of note, the TOF goal is 2/4 twitches, rather than 0/4 (Answer B), to avoid overparalysis. Although discontinuing propofol (Answer C) can facilitate extubation, this should not be done until the patient is no longer paralyzed, is at a normal body temperature, and is ready for ventilator weaning. Finally, although rewarming can cause hyperkalemia, it is appropriate to monitor K concentrations and treat as needed. It is not appropriate to increase the insulin infusion (Answer D) to prevent hyperkalemia because this could precipitate hypoglycemia during rewarming.

8. Answer: C

Propofol is an effective sedative that does not worsen delirium, but a sedative is not needed in this patient whose RASS score is 0 (alert and calm; Answer A is incorrect). Haloperidol is an option for delirium; however, her CAM-ICU is negative, so pharmacologic treatment is not indicated at this time (Answer B is incorrect). Benzodiazepines are not indicated with a RASS score of 0 and should be avoided, when possible, to prevent adverse outcomes such as prolonged mechanical ventilation, increased ICU length of stay, and development of delirium (Answer D is incorrect). Fentanyl intravenous boluses as needed would be an appropriate analgesic for the patient's pain, given that her CPOT is elevated (Answer C is correct).

9. Answer: D

Neuromuscular blocking agents should be titrated to the minimal effective dose. Although a peripheral nerve stimulator may provide information on the level of blockade, the true therapeutic endpoint in all patients is ventilator synchrony (Answer D is correct). Clinicians must recognize that neuromuscular blocking agents do not cross the blood-brain barrier and are not useful as sedatives or analgesics. For this reason, sedatives and analgesics should be optimized before initiating neuromuscular blockade, because titrating to an RASS goal while using neuromuscular blockers is not possible (Answer C is incorrect). Adequate sedation and analgesia must be achieved before initiating a neuromuscular blocker and should continue throughout the treatment. Vecuronium, though inexpensive, accumulates in renal disease and should be avoided (Answer B is incorrect). Answer A is incorrect because analgesics and sedatives should be continued during paralysis.

10. Answer: B

Although this patient is no longer paralyzed, it would be inappropriate to re-paralyze an obviously agitated patient (Answer A is incorrect) because he or she should first be adequately sedated. Similarly, performing TOF using a peripheral nerve stimulator is unnecessary because it is obvious from the patient's movement that she is not adequately blocked (Answer D is incorrect). It is possible that the patient is agitated and tachycardic because she received neuromuscular agents without adequate sedation or analgesia. Before the paralytic is adjusted, the patient should be given an increased dose of sedation (Answer B is correct). In patients with neuromuscular blockade, it is generally better to err on the side of over-sedation than under-sedation. Answer C is incorrect; dexmedetomidine does not provide the depth of sedation required for neuromuscular blockade.

11. Answer: B

Gentamicin (Answer B) has pharmacodynamic effects (i.e., inhibits the release of acetylcholine at the nicotinic receptor), which may potentiate the action of neuromuscular-blocking agents. Piperacillin/tazobactam and norepinephrine (Answers A and C) will not prolong the effects of cisatracurium. Although hypokalemia can prolong the effects of neuromuscular blocking agents, a K concentration of 4.9 mEq/L (Answer D) will not.

12. Answer: A

Given that the patient is mechanically ventilated, SUP should be administered (Answer D is incorrect). Antacids such as magnesium hydroxide are not used to prevent stress ulcers (Answer B is incorrect). Sucralfate (Answer C) is incorrect because it has been shown inferior to histamine receptor antagonists. Efficacy of histamine receptor blockers has been shown in several

clinical trials, and famotidine would be appropriate to add for this patient (Answer A is correct).

13. Answer: B

This patient's risk factors for SUP (mechanical ventilation and hypoperfusion) are no longer present; therefore, SUP should be discontinued (Answer B). There is no reason to continue SUP until ICU (Answer A) or hospital (Answer D) discharge, and this practice just increases the risk of continuing the SUP in an outpatient without an appropriate indication. Answer C is incorrect because a poor appetite is not a risk factor for developing stress-related mucosal disease.

14. Answer: D

This patient has several risk factors for VTE, including age, respiratory failure, and a history of heart failure. For this reason, intermittent pneumatic compression (Answer A) is insufficient prophylaxis. Fondaparinux (Answer B) is contraindicated in patients with an estimated CrCl less than 30 mL/minute/1.73 m2. Enoxaparin 30 mg subcutaneously twice daily (Answer C) is not an appropriate dose for this patient, considering her reduced kidney function. Heparin (Answer D) is appropriate for preventing a VTE in high-risk patients with renal dysfunction.

15. Answer: B

Parenteral nutrition (Answer A) is not indicated in patients with a functional GI tract. Metoclopramide (Answer B) should be considered because the patient's gastric residuals exceed 250 mL (Answer B is correct). Changing to a more concentrated feed would not be indicated unless the patient were volume overloaded (Answer C is incorrect). Enteral nutrition can be continued at the current rate unless the gastric residuals exceed 500 mL despite administering a prokinetic agent (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

Hydrochloric acid infusions (Answer C) are rarely used in practice and are typically reserved for more severe alkalosis (pH greater than 7.55) that is not responding to conventional therapy. Administering D_5W (Answer B) will provide hydration but will not correct intravascular volume depletion. Acetazolamide (Answer D) would be a consideration if the metabolic alkalosis persisted after correcting the underlying problem (i.e., volume contraction). This patient's ABG and urine Cl are consistent with a saline-responsive metabolic alkalosis. In critically ill patients, the most common cause of metabolic alkalosis is volume contraction. In this case, the volume contraction is probably caused by overly aggressive diuresis. In patients receiving diuretics, the urine Cl should be measured at least 12–24 hours after the last dose. In addition, the patient is hypotensive with an elevated heart rate, which probably represents hypovolemia. This patient should receive a normal saline infusion (Answer A).

2. Answer: C

If analgesia with fentanyl is adequate, this patient needs a sedative to achieve his RASS goal. Propofol is a sedative that is easily titrated and cost-effective (Answer C is correct). Dexmedetomidine is another safe and effective option, even when used for longer than 24 hours, but it has not been shown superior to propofol in randomized controlled trials (Answer A is incorrect). Furthermore, dexmedetomidine is more expensive than propofol, and a loading dose is not recommended. Lorazepam should be avoided in patients with (or at high risk of) delirium and is not a preferred first-line agent in the guidelines (Answer B is incorrect). Haloperidol is incorrect because the patient is CAM-ICU negative (Answer D is incorrect). Haloperidol can cause further prolongation of the QTc interval and lead to torsades.

3. Answer: C

This patient meets the definition for septic shock. Treatment with 5% albumin (Answer A) is unlikely to offer additional benefit because the patient's MAP is at goal (more than 65 mm Hg). Furthermore, colloids are no more effective than crystalloids for fluid resuscitation, and a serum albumin concentration does not predict the efficacy of albumin administration. Hydrocortisone (Answer B) is incorrect because the patient is not persistently hypotensive after receiving fluids and vasopressors. Although this patient's blood pressure is responding to the infusion of dopamine, the heart rate has increased. Norepinephrine (Answer C) is correct because it has similar efficacy, but with fewer tachyarrhythmias than dopamine. Dopamine should not be reduced (Answer D) because lower doses are not renal protective.

4. Answer: B

The SSC guidelines recommend adequate fluid resuscitation with either crystalloids or colloids before adding vasopressor agents in patients with sepsis. This patient's CVP, blood pressure, heart rate, and BUN/creatinine ratio indicate that she has intravascular volume depletion and needs immediate volume replacement. Therefore, intravenous fluids with either crystalloid or colloid should be the next therapy added to this patient's regimen. Answers A and C are incorrect because fluid resuscitation should be attempted before adding vasopressors. No data favor colloids over crystalloids, and the substantial increase in cost associated with colloids precludes it from being first line; therefore, Answer D (albumin) is incorrect. Lactated Ringer solution is cost-effective and is a first-line agent per current guidelines. Answer B is correct.

5. Answer: D

Targeted temperature management (i.e., therapeutic hypothermia) improves neurologic recovery and mortality in patients who have had a cardiac arrest (Answer D is correct). Although the patient probably has a metabolic acidosis, administering sodium bicarbonate (Answer A) would not improve outcomes. Vasopressin (Answer B) is no longer recommended in the ACLS guidelines. Although acute coronary syndrome is a common cause of cardiac arrest, anticoagulation with heparin (Answer C) would be a consideration after initiating targeted temperature management. A continuous infusion of heparin does not improve mortality in patients with an acute coronary syndrome. Of note, the induction of hypothermia would not necessarily interfere with treatment plans for acute coronary syndrome (e.g., percutaneous coronary intervention).

6. Answer: D

The cooling phase of therapeutic hypothermia may cause an intracellular shift of potassium, leading to decreased serum potassium on laboratory results. During the rewarming phase, an extracellular shift occurs, placing the patient at risk of hyperkalemia (Answer A is incorrect). Paralytics are not mandatory for shivering prevention during the rewarming phase and should be avoided, if possible (Answer B is incorrect). The rewarming phase of targeted temperature management alone does not place the patient at an increased risk of seizures, so prophylaxis with phenytoin is not required (Answer C is incorrect). Answer D, frequent blood glucose monitoring, is correct.

7. Answer: C

Mechanical ventilation for more than 48 hours is an independent risk factor for stress ulcers; therefore, Answer D is incorrect because the patient has a high risk of developing a stress ulcer and should receive prophylaxis. Antacids such as magnesium hydroxide are not used to prevent stress ulcers because of their need for frequent dosing and increased adverse effects (Answer B is incorrect). Sucralfate was inferior to H2 receptor blockers in preventing clinically significant bleeding (Answer A is incorrect). Histamine-2 receptor blockers and PPIs are the two drug classes commonly used to prevent stress ulcers in critically ill patients (Answer C is correct).

8. Answer: A

The SSC suggests hydrocortisone at a dose of 200 mg per day if fluids and vasopressors cannot restore hemodynamic stability (Answer A is correct; Answer D is incorrect). Although low, random cortisol concentrations predict worse outcomes, there are no data supporting treatment of low cortisol concentrations (Answer C is incorrect). Because of the results of the most recent clinical trial and increased health care costs, a cosyntropin stimulation test is not recommended for patients with septic shock (Answer B is incorrect).

9. Answer: A

There are many ways to estimate nutritional needs in critically ill patients. In general, 25 kcal/kg is an appropriate goal caloric intake per day. The recommended protein intake for medically ill patients in the ICU is 1.2-1.5 g/kg (Answer A). Indirect calorimetry will most closely calculate caloric needs, but it does not provide information on the amount of protein needed (Answer B). Feeding at 11–14 kcal/kg is recommended for patients with obesity, but this patient's BMI is less than 30 kg/m^2 (Answer C). Prealbumin concentrations have not shown good correlation with nutritional deficits in critically ill patients and are not recommended (Answer D).

10. Answer: D

Proton pump inhibitors have been associated with an increase in ventilator-associated pneumonia (Answer A). Selective digestive decontamination is effective, but because of its adverse effects and increases in resistant bacteria, it is not in widespread use and is not part of the Institute for Healthcare Improvement ventilator bundle (Answer B). Head elevation prevents ventilator-associated pneumonia, but it should be 30–45 degrees (Answer C). Chlorhexidine is inexpensive, carries few adverse effects, is easy to administer, and is effective in the prevention of ventilator-associated pneumonia (Answer D).

11. Answer: C

A sliding-scale protocol is inappropriate as the sole therapy for hyperglycemia in the ICU (Answer A). The SSC and SCCM guidelines recommend an insulin infusion for two blood glucose values greater than 180 mg/dL (Answer C). The ideal blood glucose range for critically ill adults has yet to be determined, but a goal of 80–110 mg/dL will not improve outcomes and may increase mortality (Answer D). A target of 110–180 mg/dL prevents hyperglycemia but without an excess risk of hypoglycemia (Answer C).

12. Answer: B

Nimodipine should be administered in all patients with an aneurysmal SAH for 21 days to reduce the risk of delayed cerebral ischemia and improve neurologic outcomes (Answer B is correct). Blood pressure control is important, and the guidelines recommend using a titratable agent such as clevidipine to maintain a goal systolic blood pressure less than 160 mm Hg (Answer C is incorrect). The value of calcium antagonists other than nimodipine for vasospasm remains uncertain (Answers A and D are incorrect).

Anticoagulation

Paul P. Dobesh, Pharm.D., FCCP, BCPS, BCCP

University of Nebraska Medical Center
College of Pharmacy
Omaha, Nebraska

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Paul P. Dobesh, Pharm.D., FCCP, BCPS, BCCP

University of Nebraska Medical Center
College of Pharmacy
Omaha, Nebraska

Learning Objectives

1. Recommend a patient-specific pharmacotherapy plan to reduce the risk of stroke in patients with nonvalvular atrial fibrillation.
2. Develop a feasible pharmacologic management plan to reduce thrombotic events in patients with different valvular diseases and different types of valves.
3. Devise an evidence-based pharmacotherapy plan for preventing and treating venous thromboembolism (VTE).
4. Analyze the need for anticoagulant therapy in patients with atrial fibrillation or VTE.
5. Determine appropriate reversal strategies for patients at risk of bleeding, or actively bleeding, while receiving anticoagulation therapy.
6. Determine appropriate selection and dosing of anticoagulant therapy on the basis of patient-specific factors and drug interactions.

Abbreviations in This Chapter

AF	Atrial fibrillation
CRNM	Clinically relevant nonmajor
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
FFP	Fresh frozen plasma
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
NVAF	Nonvalvular atrial fibrillation
PCC	Prothrombin complex concentrate
4PCC	4-factor prothrombin complex concentrate
PE	Pulmonary embolism
P-gp	P-glycoprotein
PRBC	Packed red blood cell
TTR	Time in therapeutic range
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–3 pertain to the following case.

J.M. is a 72-year-old woman (height 64 inches, weight 57 kg) who presents to the hospital with nonvalvular atrial fibrillation (NVAF). After her heart rate is controlled with metoprolol, she is asymptomatic. She also has hypertension, dyslipidemia, and depression. Her current medications include metoprolol 100 mg twice daily, enalapril 10 mg twice daily, and citalopram 20 mg daily. Her heart rate is currently 78 beats/minute and blood pressure is 134/86 mm Hg. Her serum creatinine (SCr) is 0.8 mg/dL and creatinine clearance (CrCl) is 60 mL/minute/1.73 m^2; she has normal hepatic function.

1. Which best depicts J.M.'s CHA_2DS_2-VASc score and HAS-BLED score?
   A. CHA_2DS_2-VASc score of 1 and a HAS-BLED score of 1.
   B. CHA_2DS_2-VASc score of 3 and a HAS-BLED score of 1.
   C. CHA_2DS_2-VASc score of 5 and a HAS-BLED score of 4.
   D. CHA_2DS_2-VASc score of 3 and a HAS-BLED score of 2.

2. Which is the most appropriate stroke prevention strategy for J.M.?
   A. Aspirin 325 mg once daily.
   B. Rivaroxaban 20 mg once daily.
   C. Apixaban 2.5 mg twice daily.
   D. Edoxaban 30 mg once daily.

3. J.M. was initiated on dabigatran and, 3 months later, is involved in a motor vehicle accident resulting in an intracranial hemorrhage. Which is the most appropriate reversal strategy for J.M.?
   A. Protamine.
   B. Fresh frozen plasma (FFP).
   C. Andexanet alfa.
   D. Idarucizumab.

Questions 4 and 5 pertain to the following case.

B.T. is 68-year-old man (height 72 inches, weight 96 kg) who recently underwent aortic valve replacement with a bioprosthetic valve and is recovering well. He also has hypertension, dyslipidemia, systolic heart failure, and a history of sustained ventricular tachycardia. His current medications include carvedilol 25 mg twice daily, lisinopril 10 mg daily, furosemide 40 mg daily, amiodarone 400 mg daily, and atorvastatin 80 mg daily. His CrCl is

40 mL/minute/1.73 m^2, his hepatic function is normal, and his other laboratory data are within normal limits.

4. Which is the most appropriate antithrombotic regimen for B.T.?
   A. Aspirin 81 mg daily.
   B. Warfarin 7.5 mg daily to an international normalized ratio (INR) of 2.5–3.5.
   C. Apixaban 5 mg twice daily.
   D. Dabigatran 150 mg twice daily.

5. Which best depicts how long B.T. should receive therapy?
   A. At least 1 month.
   B. At least 3 months.
   C. At least 1 year.
   D. Indefinitely.

Questions 6 and 7 pertain to the following case.
M.R. is a 51-year-old woman (height 65 inches, weight 98 kg, body mass index [BMI] 36 kg/m^2) who presents to the emergency department with pain, swelling, and redness in her right leg up into her thigh. She also has some shortness of breath and pain in the middle of her chest. She reports that she had a hysterectomy about 2 weeks ago and has not been moving around much at home in the past 2 weeks. On physical examination, her right leg is warmer than the left and tender to touch. Her cardiac examination appears normal, with vital signs of heart rate of 80 beats/minute, blood pressure 146/96 mm Hg, respiratory rate 20 breaths/minute, and oxygen saturation 92% on room air. Her initial laboratory information includes a positive D-dimer, a negative troponin, and a CrCl of 65 mL/minute/1.73 m^2. Duplex ultrasound detects a right femoral-popliteal deep venous thrombosis (DVT), and computed tomography (CT) reveals a pulmonary embolism (PE). Her other conditions include hypertension, diabetes mellitus, and dyslipidemia. She also reports smoking 1 pack/day of cigarettes for the past 30 years. Her current medications include lisinopril 10 mg daily, chlorthalidone 25 mg daily, metformin 1000 mg twice daily, pravastatin 40 mg daily, and hydrocodone 5 mg/acetaminophen 500 mg every 6 hours as needed for pain.

6. Which best depicts M.R.'s number of venous thromboembolism (VTE) risk factors?
   A. 3.
   B. 4.
   C. 5.
   D. 6.

7. Which is the most appropriate treatment strategy for M.R.?
   A. Enoxaparin 100 mg every 12 hours and dabigatran 150 mg twice daily; after 5 days, enoxaparin can be discontinued.
   B. Rivaroxaban 15 mg twice daily for 7 days, followed by 20 mg once daily.
   C. Enoxaparin 100 mg every 12 hours for 5 days; then initiate edoxaban 60 mg once daily.
   D. Unfractionated heparin (UFH) 4000-unit bolus, followed by 1000 units/hour and warfarin 7.5 mg to an INR of 2.0–3.0, discontinuing UFH when a therapeutic INR is reached.

8. T.G. (weight 125 kg) is admitted for the treatment of a DVT with a PE. He is given a 10,000-unit bolus of UFH and initiated on an infusion of 2250 units/hour. Twelve hours into the infusion, he begins to vomit blood. Which is the most appropriate protamine dose for T.G.?
   A. 100 mg.
   B. 50 mg.
   C. 39 mg.
   D. 22.5 mg.

9. P.M. recently had knee replacement surgery. She has normal renal and hepatic function. Which is the most appropriate regimen for preventing VTE in P.M.?
   A. Dabigatran 110 mg, followed by 220 mg once daily.
   B. Enoxaparin 40 mg subcutaneously once daily.
   C. Fondaparinux 2.5 mg subcutaneously once daily.
   D. Edoxaban 60 mg once daily.

I. STROKE PREVENTION IN NONVALVULAR ATRIAL FIBRILLATION

A. Introduction
   1. Atrial fibrillation (AF) is the most common sustained cardiac dysrhythmia, affecting 2.7–6.1 million Americans.
   2. Incidence increases with age.
      a. Around 1% of patients with AF are younger than 60.
      b. Around 12% of patients with AF are 75–84 years of age.
      c. More than 33% of patients with AF are 80 or older.
   3. Accounts for more than 500,000 hospital discharges annually in the United States and significant health care costs

B. Pathophysiology
   1. Etiology
      a. Typically related to structural heart disease such as coronary artery disease or heart failure or other cardiogenic issues such as hypertension
      b. Valvular heart disease
      c. Noncardiogenic causes: Hyper- or hypothyroid disease, acute infection, excessive alcohol intake, post-surgery, and PE
   2. Rhythm
      a. AF is supraventricular tachyarrhythmia.
      b. Incomplete conduction of supraventricular impulses
      c. Conduction through the AV node is erratic and is revealed by the electrocardiogram as an irregularly irregular rhythm.
   3. Thrombosis
      a. Incomplete conduction of supraventricular impulses creates a lack of atrial contraction.
      b. Incomplete emptying of the cardiac chambers during systole increases the rate of blood pooling in the atria, most notably in the left atrial appendage.
      c. 90% of thromboses occur in the left atrial appendage and 10% in the left atrium.
      d. Blood stasis is associated with the increased formation of mural thrombi, which may cause arterial embolization, or stroke, if dislodged by a return to normal sinus rhythm or by the shearing forces from turbulent blood flow through the chambers.

C. Definitions
   1. Paroxysmal AF: AF that terminates spontaneously or with intervention within 7 days
   2. Persistent AF: Continuous AF that is sustained more than 7 days
   3. Longstanding persistent AF: Continuous AF for more than 12 months
   4. Permanent AF: Decision of the patient and clinician to stop further attempts to restore and/or maintain normal sinus rhythm and remain in AF
   5. NVAF: When discussing the role of direct oral anticoagulants (DOACs), NVAF represents patients without moderate or severe mitral stenosis and those with mechanical heart valves, including patients receiving transcatheter aortic valve replacement (TAVR).

D. Stroke
   1. NVAF increases the risk of stroke by 5-fold compared with patients without AF.
   2. AF is responsible for 15%–20% of all strokes.

3. Risk stratification (only for patients with NVAF)
   a. $CHADS_2$ score
      i. 6 possible points depending on risk factors (Table 1)
      ii. Risk of ischemic stroke is 1.9%–18.2%, depending on score (Table 2).
      iii. Limited by ability to determine who is truly at low or intermediate risk because those with scores of 0 or 1 suggest a risk of almost 2%–3% (Table 2)
   b. CHA_2DS_2-VASc score
      i. 9 possible points based on risk factors (Table 1)
      ii. Adds risk factors of age 65–74, female sex, and history of other vascular disease
      iii. Improves predictive value of who is truly at low risk (score of 0 = 0% risk) and intermediate risk (score of 1 = 1.3% risk)
      iv. Guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society, European Society of Cardiology, and American College of Chest Physicians (ACCP) recommend using the CHA_2DS_2-VASc score to determine the need for anticoagulant therapy in patients with NVAF (Table 3; Table 4).

Table 1. Risk Stratification for Ischemic Stroke in Patients with NVAF

$CHADS_2$ Score		CHA_2DS_2-VASc Score	
Congestive heart failure[a]	1	Congestive heart failure[a]	1
Hypertension	1	Hypertension	1
Age ≥ 75	1	Age ≥ 75	2
Diabetes mellitus	1	Diabetes mellitus	1
Previous stroke or TIA	2	Previous stroke or TIA	2
		Vascular disease (prior MI, PAD, aortic plaque)	1
		Age 65–74	1
		Sex category (female)	1

[a]Heart failure as a risk factor represents those with an ejection fraction ≤ 40%.

MI = myocardial infarction; NVAF = nonvalvular atrial fibrillation; PAD = peripheral arterial disease; TIA = transient ischemic attack.

Table 2. Adjusted Stroke Rate per Year Based on $CHADS_2$ and CHA_2DS_2-VASc Scores

Score	$CHADS_2$ Adjusted Stroke Rate (%/yr)	CHA_2DS_2-VASc Adjusted Stroke Rate (%/yr)	Risk Category
0	1.9	0	Low
1	2.8	1.3	Intermediate
2	4.0	2.2	High
3	5.9	3.2	
4	8.5	4.0	
5	12.5	6.7	
6	18.2	9.8	
7	—	9.6	
8	—	6.7	
9	—	15.2	

Table 3. AHA/ACC/Heart Rhythm Society Guideline Recommendations for Antithrombotic Therapy in Patients with NVAF Based on CHA_2DS_2-VASc Score[a]

CHA_2DS_2-VASc Score of 0 in men or 1 in women	CHA_2DS_2-VASc Score of 1 in men or 2 in women	CHA_2DS_2-VASc Score of 2 in men or 3 in women
Reasonable to omit antithrombotic therapy or consider aspirin	Consider no antithrombotic therapy, oral anticoagulation, or aspirin	Oral anticoagulant therapy is indicated. DOAC over warfarin in DOAC-eligible patients

[a]AHA/ACC/Heart Rhythm Society guidelines

DOAC = direct oral anticoagulant.

Table 4. ACCP Guideline Recommendations for Patients with AF[a]

Recommendation	Quality of Evidence
Use a risk factor approach for assessing a patient's stroke risk instead of a categorical approach of low, moderate, or high risk. Recommend use of the CHA_2DS_2-VASc score	Moderate
Antithrombotic therapy for patients with one or more non-sex CHA_2DS_2-VASc stroke risk factors (score ≥ 1 in a male or ≥ 2 in a female)	Moderate
A bleeding risk assessment at every patient contact should initially focus on potentially modifiable bleeding risk factors (e.g., blood pressure, medications, treat gastric ulcer, optimize renal function)	Low
Recommend use of the HAS-BLED score. Those at high risk of bleeding (HAS-BLED ≥ 3) warrant more frequent and regular reviews of follow-up	Moderate
Recommend against antiplatelet therapy (monotherapy or aspirin with clopidogrel) for stroke prevention alone, regardless of stroke risk	Moderate
For patients eligible for oral anticoagulation, recommend DOACs over VKA	Moderate
Patients taking a VKA with a consistently low time in therapeutic range (TTR < 65%), recommend interventions to improve TTR or changing to a DOAC	Moderate
Patients with AF > 48 hr or unknown duration, undergoing elective cardioversion should receive therapeutic anticoagulation with well-managed VKA (INR 2.0–3.0) or a DOAC for at least 3 wk before cardioversion or a transesophageal echocardiography–guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation	Moderate
Patients with AF > 48 hr or unknown duration undergoing elective cardioversion should receive therapeutic anticoagulation with a VKA or a DOAC for at least 4 wk after successful cardioversion rather than no anticoagulation, regardless of their baseline risk of stroke	Moderate
Patients with AF and acute ischemic stroke should receive long-term oral anticoagulation unless contraindicated	High

[a]Recommendations listed only include those considered "strong" by ACCP. Recommendations considered "weak" or "ungraded" are controversial because of limited quality and quantity of data and are not listed.

ACCP = American College of Chest Physicians; AF = atrial fibrillation; TTR = time in therapeutic range; VKA = vitamin K antagonist.

c. HAS-BLED score (Table 5)
   i. 9-point scale to assess risk of major bleeding with warfarin in patients with NVAF
   ii. Few patients have a score of 3 or greater.
   iii. Should not be used to determine who does not receive therapy, but more to balance the risk of stroke with the risk of bleeding
   iv. Predictive value is inconsistent and unreliable with DOACs.

Table 5. Components and Bleeding Rates of the HAS-BLED Score

Risk Factors		Points
Hypertension (systolic BP > 160 mm Hg)		1
Abnormal renal or liver function[a]		1 or 2
History of stroke		1
History of bleeding[b]		1
Labile INRs[c]		1
Older adults (age > 65)		1
Drugs or alcohol excess[d]		1 or 2
Score	**% of Patients**	**Risk of Major Bleeding/Yr**
0	26	1.1%
1	42	1.0%
2	24	1.9%
3	6	3.7%
4	2	8.7%
5	< 1	12.5%
> 5	< 1%	Undetermined

[a]1 point for renal and 1 point for liver.

Renal = chronic dialysis, renal transplantation, or SCr ≥ 2.26 mg/dL

Liver = chronic hepatic disease, bilirubin > 2 x the upper limit of normal (ULN), in association with AST/ALT/Alk Phos > 3 x the ULN.

[b]History of bleeding or predisposition to bleeding such as a bleeding diathesis or anemia.

[c]Unstable/high INRs or time in therapeutic range < 60%.

[d]Drugs include antiplatelet or nonsteroidal anti-inflammatory drugs = 1 point; alcohol excess is ≥ 8 alcohol drinks/wk = 1 point.

BP = blood pressure.

E. Anticoagulant Therapy
   1. Warfarin
      a. Vitamin K antagonist (VKA) – Racemic mixture
         i. Inhibits vitamin K recycling by inhibiting vitamin K epoxide reductase > vitamin K reductase, preventing γ-carboxylation of clotting factors II, VII, IX, and X, leaving these factors unable to bind to phospholipid membranes and unable to take part in coagulation
         ii. Also inhibits carboxylation and activation of natural anticoagulants protein C and protein S
         iii. *S*-warfarin is about 5 x more potent than *R*-warfarin.
      b. Several trials have shown a 70%–80% risk reduction in stroke and systemic embolism with warfarin therapy compared with placebo.
      c. Dosing for NVAF is based on requirements to achieve an INR goal of 2.0–3.0.
      d. Initial starting dose is typically 5 mg daily, but doses of up to 10 mg daily may be started in hospitalized patients. A lower starting dose (2–3 mg daily) should be considered in patients with the following: advanced age, low body weight, drug interactions, malnourishment, heart failure, hyperthyroid state, low albumin or liver disease, selected ethnic groups (e.g., Asians)
         i. Dosing algorithms are available to help with initiating therapy.
         ii. Using pharmacogenomic data can achieve a faster therapeutic INR and fewer INRs of 4 or less but has not reduced thrombotic or bleeding events. Therefore, using pharmacogenomic data is not part of standard of care.
         iii. In patients receiving a parenteral direct thrombin inhibitor or in lupus cases when the INR is not reflective of dosing, a factor VII or X concentration has been used with some success. A chromogenic factor X assay is likely the most reliable mechanism to measure the anticoagulant activity of warfarin in these patients, especially with INR values greater than 3.0.

iv. Consider half-lives of inhibited clotting factors: factor VII = 6 hours, factor XI =24 hours, factor X = 36 hours, factor II = 72 hours
v. Functional clotting factors already produced must "run their course" and cannot be inhibited with higher doses, regardless of the INR.

c. Follow-up INR monitoring
i. INR values on a specific day are the result of warfarin doses taken over the previous 3–4 days, and dosing changes made on a specific day are not fully represented in the INR for 3–5 days. It takes 5–7 days to see the full effect of a stable warfarin dose.
ii. If the INR is out of the therapeutic range in the outpatient setting, increase or decrease the cumulative weekly dose by 5%–20%, depending on the INR; if the INR is greater than 4.5, consider holding one or two doses before resuming at the reduced dose.
iii. In the setting of continuous enteral feeding, consider holding the feeds 1 hour before and after the dose.
iv. If the INR is previously stable or therapeutic and a single out-of-range INR is 0.5 or less above or below the therapeutic range, current dosing can be continued; the INR should be rechecked within 1–2 weeks.
v. In general, no need to adjust dose if INR is within 0.1 of goal, but would monitor more closely (especially if below goal)
vi. If the INR decreases to 1.8 or less, the risk of ischemic stroke in NVAF increases by 60%, whereas the risk of bleeding does not significantly increase until the INR is greater than 4.0 (better to be a little high than a little low).
vii. VKA therapy is well managed when the individual patient's time in therapeutic range (TTR) is greater than 65%–70%. If this level of TTR is not achieved, strategies should be implemented to improve the patient's TTR (e.g., more frequent monitoring, better control of diet, alcohol, drug interactions, referral to a dedicated anticoagulation clinic), or therapy should be changed to a DOAC.

f. Drug interactions
i. Reduced warfarin absorption (e.g., cholestyramine, sucralfate)
ii. Enzyme induction producing a reduced INR and warfarin effect, increased risk of thrombosis (e.g., phenytoin, phenobarbital, carbamazepine, rifampin, St. John's wort)
iii. Enzyme inhibition producing an increased INR and warfarin effect, increased risk of bleeding
(a) *S*-warfarin mainly metabolized by cytochrome P450 (CYP) 2C9 > CYP3A4 (e.g., metronidazole, trimethoprim/sulfamethoxazole, fluconazole, isoniazid, fluoxetine, sertraline, amiodarone)
(b) *R*-warfarin mainly metabolized by CYP1A2 and CYP3A4 > CYP2C19 (e.g., clarithromycin, erythromycin, azole antifungals, fluoxetine, amiodarone, cyclosporine, sertraline, grapefruit juice, ciprofloxacin, protease inhibitors, diltiazem, verapamil, isoniazid, metronidazole)
iv. Antiplatelet agents through a pharmacodynamic effect (e.g., aspirin, $P2Y_{12}$ inhibitors, nonsteroidal anti-inflammatory drugs, fish oil, gingko, garlic)
v. Agents that affect warfarin clearance (e.g., amiodarone, propafenone, cimetidine)
vi. Agents that reduce vitamin K synthesis in the intestinal flora (e.g., antibiotics)

g. Drug-disease interactions
i. Increased clotting factor consumption (e.g., hyperthyroid state, fever)
ii. Reduced warfarin metabolism (e.g., heart failure, liver disease)
iii. Reduced clotting factor production (e.g., liver disease)

h. Drug-food interactions
i. Recommended dietary intake of vitamin K is 80 mcg/day.
ii. Wide variety of vitamin K in various foods
iii. Goal is to remain consistent with intake of vitamin K–containing foods while the patient is receiving warfarin therapy, which may be challenging for some patients.

2. Dabigatran
    a. Mechanism of action and pharmacologic properties (Table 6)
    b. Dosing recommendations (Table 7). Reduced dose of 75 mg twice daily has not been evaluated in clinical trials. Reduced dose of 110 mg twice daily is not indicated for patients with NVAF in the United States, but this is used in Canada and Europe.
    c. Evaluated in the RE-LY trial compared with dose-adjusted warfarin
    d. In addition to bleeding, dyspepsia is a common adverse effect, occurring in about 10% of patients and contributing to significantly higher rates of drug discontinuation at 1 year and 2 years in the RE-LY trial.
    e. Stability: Once the bottle is opened, the medication should be used within 4 months to maintain appropriate potency, and capsules cannot be placed in a pillbox.
    f. Drug interactions based on P-glycoprotein (P-gp) (Table 7)
    g. Capsules should not be opened because this results in a 75% increase in bioavailability.
    h. Converting to and from dabigatran to and from other anticoagulants (Box 1)

Box 1. Dabigatran Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Dabigatran to Warfarin	
CrCl ≥ 50 mL/min/1.73 m^2	Start warfarin 3 days before discontinuing dabigatran
CrCl 31–50 mL/min/1.73 m^2	Start warfarin 2 days before discontinuing dabigatran
CrCl 15–30 mL/min/1.73 m^2	Start warfarin 1 day before discontinuing dabigatran
CrCl < 15 mL/min/1.73 m^2	No dosing recommendations are available
	Reasonable to initiate warfarin 1 day before discontinuing dabigatran
Converting from Warfarin to Dabigatran	
Discontinue warfarin and start dabigatran when the INR is < 2.0[a]	
Converting Between Dabigatran and Parenteral Anticoagulants	
• Start dabigatran 0–2 hr before the next dose of the parenteral drug was to have been administered (e.g., LMWH) or when a continuously administered parenteral drug is discontinued (e.g., IV UFH) • For patients currently taking dabigatran, wait 12 hr (CrCl > 30 mL/min/1.73 m^2) or 24 hr (CrCl < 30 mL/min/1.73 m^2) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant. • Note: High dabigatran concentrations can occur in severe renal impairment, and effects last for several days. A thrombin time can be used to determine when the effects of dabigatran are dissipating.	

[a]Because dabigatran can contribute to an increased INR, the INR will better reflect warfarin's effect after dabigatran has been discontinued for at least 2 days.

IV = intravenous(ly); LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

3. Rivaroxaban
    a. Mechanism of action and pharmacologic properties (Table 6)
    b. Dosing recommendations (Table 7). Reduced dose of 15 mg once daily is available and should be taken with food. Used in around 20% of the patients in the ROCKET-AF trial
    c. Evaluated in the ROCKET-AF trial compared with dose-adjusted warfarin
    d. Drug interactions
        i. Strong CYP3A4 and P-gp inhibitors and inducers (Table 7)
        ii. The rivaroxaban package label has a warning for use of moderate CYP3A4 and P-gp inhibitors (e.g., amiodarone, verapamil, diltiazem, erythromycin, dronedarone, cimetidine) in patients with a CrCl of 15–80 mL/minute/1.73 m^2, given increased rivaroxaban concentrations in pharmacokinetic studies. An analysis of patients receiving these agents with rivaroxaban with this level of renal function from the ROCKET-AF trials did not show an increased risk of bleeding.

e. Converting to and from rivaroxaban to and from other anticoagulants (Box 2)

Box 2. Rivaroxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Rivaroxaban to Warfarin
Discontinue rivaroxaban, and begin both a parenteral anticoagulant and warfarin when the next dose of rivaroxaban would have been taken. Discontinue the parenteral anticoagulant when INR > 2.0
Converting from Rivaroxaban to Anticoagulants(with rapid onset) Other than Warfarin
Discontinue rivaroxaban, and give the first dose of the other anticoagulant (oral or parenteral; other than warfarin) when the next rivaroxaban dose would have been taken
Converting from Warfarin to Rivaroxaban
Discontinue warfarin and initiate rivaroxaban once INR < 3.0
Converting from Anticoagulants (with rapid onset) Other than Warfarin to Rivaroxaban
Begin rivaroxaban 0–2 hr before the next scheduled evening administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start rivaroxaban at the same time

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

4. Apixaban
   a. Mechanism of action and pharmacologic properties (Table 6)
   b. Dosing recommendations (Table 7)
      i. Reduced dose of 2.5 mg twice daily is available and used in about 5% of the patients in the ARISTOTLE trial.
      ii. Data suggest that the reduced dose is being used in many patients (up to 30%), with most not meeting the trial criteria for the reduced dose. One study suggests this is associated with a 20% increased risk of ischemic stroke.
   c. Evaluated in the ARISTOTLE trial compared with dose-adjusted warfarin
   d. Drug interactions are associated with strong CYP3A4 and P-gp inhibitors and inducers (Table 7).
   e. Converting to and from apixaban to and from other anticoagulants (Box 3)

Box 3. Apixaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Apixaban to Warfarin
Discontinue apixaban, and begin both a parenteral anticoagulant and warfarin when the next dose of apixaban would have been taken. Discontinue the parenteral anticoagulant when INR > 2.0
Converting from Apixaban to Anticoagulants (with rapid onset) Other than Warfarin
Discontinue apixaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of apixaban
Converting from Warfarin to Apixaban
Warfarin should be discontinued and apixaban initiated when INR < 2.0
Converting from Anticoagulants (with rapid onset) Other than Warfarin to Apixaban
Begin apixaban 0–2 hr before the next scheduled administration of the drug (e.g., LMWH or non-warfarin oral anticoagulant), and do not administer the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start apixaban at the same time

5. Edoxaban
    a. Mechanism of action and pharmacologic properties (Table 6)
    b. Dosing recommendations (Table 7). Reduced dose of 30 mg once daily is available. Used in around 25% of the patients in the ENGAGE-AF trial
    c. Evaluated in the ENGAGE-AF TIMI 48 trial compared with dose-adjusted warfarin
    d. Drug interactions are associated with P-gp (Table 7).
    e. Converting to and from edoxaban to and from other anticoagulants (Box 4)

Box 4. Edoxaban Conversion Strategies to and from Oral and Parenteral Anticoagulants

Converting from Edoxaban to Warfarin
Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. The INR must be measured at least weekly and just before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2.0 is achieved, edoxaban should be discontinued and warfarin continued
Parenteral option: Discontinue edoxaban, and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and warfarin continued
Converting from Edoxaban to Anticoagulants (with rapid onset) Other than Warfarin
Discontinue edoxaban, and begin the new anticoagulant (oral or parenteral; other than warfarin) at the usual time of the next dose of edoxaban
Converting from Warfarin to Edoxaban
Discontinue warfarin and start edoxaban when the INR is ≤ 2.5
Converting from Anticoagulants (with rapid onset) Other than Warfarin to Edoxaban
Discontinue the other oral anticoagulant (other than warfarin) or LMWH, and begin taking edoxaban at the usual time of the next dose of the other anticoagulant. For UFH administered by continuous infusion, stop the infusion and start edoxaban 4 hr later

Table 6. DOAC Pharmacologic Properties

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Bioavailability	3%–7%	66% without food, 80%–100% with food	50%	62%
Onset of anticoagulant activity	1.5 hr	2–4 hr	2–3 hr	1–2 hr
Half-life[a]	12–17 hr	9–13 hr	12 hr	9–10 hr
Renal clearance	80%	36%	27%	50%
Protein binding	35%	90%	87%	55%
Removed by dialysis	Yes	No	No	No
P-gp transport	Yes	Yes	Yes	Yes
Hepatic metabolism	None	CYP 3A4/5 and CYP2J2	CYP3A4/5	Minimal (4% CYP3A4/5)

[a]Half-life can be increased in patients with severe illness with renal and/or hepatic failure.

Table 7. Dosing of DOACs in NVAF

Agent	Standard Dosing	Dose Adjustment[a]	Avoid Use[a]
Dabigatran	150 mg twice daily	75 mg twice daily • CrCl 15–30 mL/min/1.73 m^2 • CrCl 30–50 mL/min/1.73 m^2 with ketoconazole or dronedarone	• CrCl < 15 mL/min • Dialysis • CrCl 15–30 mL/min/1.73 m^2 with amiodarone, verapamil, ketoconazole, dronedarone, diltiazem, and clarithromycin • Rifampin
Rivaroxaban	20 mg once daily with meals	15 mg once daily with meals • CrCl 15–50 mL/min/1.73 m^2 • Dialysis[b]	• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
Apixaban	5 mg twice daily	2.5 mg twice daily • Two of three criteria (age ≥ 80 yr, weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL) • Use with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan) • Dialysis?[b,c]	• Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • If on 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
Edoxaban	60 mg once daily	30 mg once daily • CrCl 15–50 mL/min/1.73 m^2	• CrCl > 95 mL/min/1.73 m^2 • CrCl < 15 mL/min/1.73 m^2 • Dialysis • Rifampin

[a]CrCl in the DOAC trials was calculated using Cockcroft-Gault equation with total body weight.

[b]Data in the package label for dosing for rivaroxaban and apixaban in the setting of dialysis are from eight-patient single-dose pharmacokinetic studies, with no data supporting safety or efficacy available.

[c]The apixaban package label suggests a dose of 5 mg twice daily in patients receiving dialysis with age < 80 and weight > 60 kg. A study with multiple days of apixaban administration in patients receiving dialysis showed about a 2-fold increase in Cmax and area under the curve using 5 mg twice daily and suggests that the 2.5-mg twice-daily dose can be considered.

6. Trial results
    a. Primary efficacy end point – Stroke or systemic embolism
        i. All agents noninferior to warfarin – Primary end point of all the trials
        ii. Dabigatran and apixaban were superior to warfarin in the intention-to-treat analysis.
        iii. Rivaroxaban and edoxaban were superior to warfarin in the per-protocol analysis.
    b. Hemorrhagic stroke – All agents significantly better than warfarin. This is the main benefit of a DOAC over warfarin across all trials.
    c. Ischemic stroke – Only dabigatran significantly better than warfarin

d. Major bleeding
    i. Apixaban and edoxaban were significantly safer than warfarin.
    ii. Dabigatran and rivaroxaban had safety similar to warfarin.
e. All-cause mortality
    i. Only apixaban significantly reduced mortality compared with warfarin (p=0.01).
    ii. All agents provided about a 10% relative reduction in mortality.

7. Controversies and considerations
    a. Major differences in the trials (Table 8) prevent concluding that one agent has superior efficacy or safety over any other. The AHA/ACC/Heart Rhythm Society, European Society of Cardiology, and American College of Chest Physicians (ACCP) guidelines do not prefer one DOAC to another.
    b. Patient risk
        i. The mean $CHADS_2$ score in the ROCKET-AF trial was 3.5 compared with 2.1 in the RE-LY and ARISTOTLE trials. The $CHADS_2$ score in ENGAGE-AF was 2.8.
        ii. Varied results may be due to studying different risks of patients compared with using a different DOAC.
    c. Ischemic stroke
        i. Although dabigatran was the only agent that significantly reduced ischemic stroke, the RE-LY trial was the only unblinded study.
        ii. Previous studies with ximelagatran have shown that blinded warfarin (SPORTIF V) performs better than unblinded warfarin (SPORTIF III) by almost a 1% absolute difference.
        iii. Had the RELY trial been blinded, the outcome might have been different.
    d. The difference between the intention-to-treat analysis and the per-protocol analysis is only 28 patients in the ROCKET-AF trial of rivaroxaban (0.2% of the overall trial population) and only 47 patients in the ENGAGE-AF trial of edoxaban (0.3% of the overall trial population). Both agents were superior to warfarin in this analysis.
    e. Absolute difference in the primary end point in the intention-to-treat analysis was 0.3% in both the ROCKET-AF trial with rivaroxaban and the ARISTOTLE trial with apixaban. Differing statistical findings may be because the ARISTOTLE trial had around 4000 more patients in the overall study.
    f. All agents reduce mortality by about 10%, with only apixaban achieving statistical significance. May be because the ARISTOTLE trial had about 2000 more patients per arm than all of the other trials
    g. The lower bleeding rates with apixaban and edoxaban may be because of the shorter assessment of bleeding events (2 days and 3 days, respectively) compared with dabigatran and rivaroxaban. All the NVAF DOAC trials used the ISTH definition of major bleeding, or with slight modification. Part of this definition includes a hemoglobin decrease of 2 g/dL or more. Although this was included in all the trials, only in the ARISTOTLE trial with apixaban did this decrease have to occur within 24 hours. This may explain why gastrointestinal bleeding was not different in this trial because these are typically slower bleeds.
    h. Although the time in therapeutic range was lower in the ROCKET-AF trial with rivaroxaban than in other trials, this trial had the highest-risk patients (more difficult to control INR) and was the only trial that did not provide the investigators with a protocol to follow (wanted to evaluate real-world practice). Regardless, analysis has shown that time in therapeutic range with warfarin did not influence the study outcomes for any of the agents other than perhaps dabigatran.

Table 8. Comparison of Trial Characteristics of DOACs vs. Warfarin

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Study drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study size	18,113 (3 arms)	14,264 (2 arms)	18,201 (2 arms)	21,105 (3 arms)
Double-blind	No	Yes	Yes	Yes
Previous VKA use (%)	50	62	57	59
$CHADS_2$ score				
Mean	2.1	3.5	2.1	2.8
0–1 (%)	32	0	34	—
2 (%)	36	13	36	77 (≤ 3)
3–6 (%)	32	87	30	23 (4–6)
Previous stroke or TIA (%)	20	55	19	28
Protocol to manage INR	Yes	No	Yes	Yes
Mean TTR (%)	64	55	62	65
Median TTR (%)	NR	58	66	68
Median follow-up (yr)	2.0	1.9	1.8	2.8

NR = not reported.

F. Antiplatelet Therapy – Only for patients who cannot tolerate anticoagulants
   1. Aspirin
      a. Historically used in low or intermediate thrombosis risk of stroke, but also in patients at high risk of bleeding (when anticoagulation therapy is contraindicated)
      b. Meta-analysis of eight trials comparing aspirin with placebo or no therapy in 4876 patients with NVAF
         i. Doses ranged from 25 mg twice daily to 1300 mg once daily.
         ii. Primary prevention aspirin had an absolute reduction of 0.8%.
         iii. Secondary prevention aspirin had an absolute reduction of 2.5%.
         iv. Benefit of aspirin from one trial drives these results.
      c. Only the SPAF-1 (Stroke Prevention in Atrial Fibrillation) trial has shown a benefit of aspirin in reducing the risk of ischemic stroke in patients with NVAF.
         i. Dose was 325 mg daily.
         ii. Only effective in patients 75 and younger
      d. Apixaban 5 mg twice daily was compared with aspirin in patients who were unsuitable for warfarin therapy in the AVERROES trial.
         i. Trial was stopped early because of the significantly better efficacy of apixaban compared with aspirin.
         ii. No difference in major bleeding
         iii. 65% of patients received an aspirin dose of 81 mg daily, and only 2% received an aspirin dose of 324 mg.
         iv. Trial shows that apixaban (and likely the other DOACs) is safe in patients who are unsuitable for warfarin therapy and should replace aspirin as the traditional alternative to warfarin therapy in these patients.

2. Aspirin plus clopidogrel – Evaluated in the two ACTIVE trials (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events). Patients with NVAF and at least one risk factor for stroke
   a. ACTIVE – W (compared with warfarin)
      i. Aspirin 75–100 mg daily plus clopidogrel 75 mg daily compared with dose-adjusted warfarin to an INR of 2.0–3.0
      ii. Trial was stopped early because of the superior efficacy of warfarin.
      iii. Aspirin and clopidogrel were inferior to warfarin (5.6% vs. 3.9%; $p<0.001$) for stroke, systemic embolism, MI, and vascular death.
      iv. No difference in major bleeding, but significantly more minor bleeding with aspirin and clopidogrel than with warfarin
   b. ACTIVE – A (compared with aspirin)
      i. Aspirin 75–100 mg daily plus clopidogrel 75 mg daily compared with aspirin alone if they were not candidates for, or refused anticoagulation with, warfarin
      ii. Aspirin plus clopidogrel was superior to aspirin alone (6.8% vs. 7.6%; $p=0.01$).
      iii. Reduction in the primary end point was driven by reductions in ischemic stroke and MI.
      iv. Significant increase in major and minor bleeding with the use of dual antiplatelet therapy
      v. Subgroup analysis identified that patients at intermediate risk of stroke ($CHADS_2$ score = 1) derived the most benefit from adding clopidogrel to aspirin.

G. Patients with NVAF Who Need Percutaneous Coronary Intervention (require triple antithrombotic therapy)
   1. Although the risk of major bleeding with warfarin therapy in patients with AF is around 2% per year, patients receiving warfarin, aspirin, and clopidogrel have a major bleeding rate of around 8% per year.
   2. Approaches that have not been prospectively evaluated include the following:
      a. A target INR of 2.0–2.5 instead of 2.0–3.0
      b. Aspirin 81 mg instead of higher doses
      c. Clopidogrel instead of ticagrelor or prasugrel because both newer $P2Y_{12}$ inhibitors have more non-coronary artery bypass graft major bleeding than clopidogrel
      d. Trying to use bare metal stents and/or keeping the duration of dual antiplatelet therapy to a minimum
   3. WOEST trial (n=573) compared triple therapy (warfarin, clopidogrel 75 mg daily, and aspirin 80–100 mg daily) with double therapy (same therapy but without the aspirin).
      a. The primary end point of any bleeding was significantly reduced by a relative 64% using double therapy compared with triple therapy. Major bleeding was reduced by 44%, but this was not significant.
      b. There was a significant 40% relative reduction in major cardiac events with double therapy compared with triple therapy, which was driven by a reduction in noncardiac death. The incidence of MI, stent thrombosis, stroke, and target-vessel revascularization was no different.
      c. These data are encouraging, but they are from a small, open-label trial done in the Netherlands and Belgium.
   4. PIONEER AF-PCI trial (n=2124) compared three groups for 12 months:
      a. Group 1 received rivaroxaban 15 mg once daily (or 10 mg once daily if CrCl was 30–50 mL/minute/1.73 m^2) plus clopidogrel 75 mg daily (only 2% received prasugrel and 5% ticagrelor) for 12 months.
      b. Group 2 received rivaroxaban 2.5 mg twice daily plus aspirin 75–100 mg daily, plus clopidogrel 75 mg daily (only 2% received prasugrel and 5% ticagrelor) for 1, 6, or 12 months. Patients who received therapy for only 1 or 6 months were then changed rivaroxaban 15 mg once daily (or 10 mg once daily if CrCl 30–50 mL/minute/1.73 m^2) plus aspirin 75–100 mg daily for the remainder of the 12 months.

   c. Group 3 represented standard care and received adjusted-dose warfarin to an INR of 2.0–3.0 plus aspirin 75–100 mg daily plus clopidogrel 75 mg daily (only 1% received prasugrel and 3% ticagrelor) for 1, 6, or 12 months. Patients who received therapy for only 1 or 6 months continued to receive warfarin and aspirin 75–100 mg daily.
   d. The primary outcome of clinically significant bleeding was significantly lower for group 1 (16.8%) and group 2 (18.0%) than for group 3 (26.7%).
   e. Although not powered to evaluate ischemic outcomes, there was no difference in the composite of cardiovascular death, MI, and stroke for group 1 (6.5%), group 2 (5.6%), and group 3 (6.0%).
5. RE-DUAL PCI trial (n=2725) compared three groups for at least 6 months.
   a. Group 1 received dabigatran 110 mg twice daily plus clopidogrel or ticagrelor for at least 12 months.
   b. Group 2 received dabigatran 150 mg twice daily plus clopidogrel or ticagrelor for at least 12 months. Older adult patients (80 years and older or 70 years and older in Japan) outside the United States were not eligible to be randomized to this group. Therefore, the comparison for this group excluded these same patients from group 3. Consequently, findings from this group do not apply to older adult patients.
   c. Group 3 represented standard care and received adjusted-dose warfarin to an INR of 2.0–3.0, plus aspirin at 100 mg or less daily, plus clopidogrel or ticagrelor. Aspirin was discontinued after 1 month in patients receiving a bare metal stent and after 3 months in patients receiving a drug-eluting stent.
   d. The primary end point of first major and clinically relevant nonmajor (CRNM) bleeding (International Society on Thrombosis and Haemostasis definition) was significantly lower for group 1 (15.4%) than for group 3 (26.9%) and was also lower for group 2 (20.2%) than for the corresponding patients in group 3 (25.7%).
   e. Although not designed to evaluate ischemic outcomes, the 5-point composite outcome of MI, stroke, systemic embolism, death, or unplanned revascularization was noninferior between group 1 (15.2%) and group 3 (13.4%) as well as for group 2 (11.8%) compared with the corresponding patients in group 3 (12.8%).
6. The AUGUSTUS trial (n=4614) compared four groups for 6 months.
   a. Group 1 received apixaban 5 mg twice daily plus clopidogrel.
   b. Group 2 received apixaban 5 mg twice daily plus clopidogrel plus aspirin 81 mg daily.
   c. Group 3 received adjusted-dose warfarin to an INR of 2.0-3.0 plus clopidogrel.
   d. Group 4 received adjusted-dose warfarin to an INR of 2.0–3.0 plus clopidogrel plus aspirin 81 mg daily.
   e. The primary end point of major or CRNM bleeding occurred significantly less often in patients receiving apixaban than in patients receiving warfarin and less commonly in patients receiving no aspirin than in patients receiving aspirin (group 1 = 7.3%, group 2 = 13.8%, group 3 = 10.9%, and group 4 = 18.7%).
   f. Although the trial was not designed to evaluate ischemic outcomes, the incidence of all-cause death or ischemic outcomes was 6.2% in groups 1 and 2, 7.3% in group 3, and 5.7% in group 4.
7. The ENTRUST-AF PCI trial (n=1506) compared two groups for 12 months.
   a. Group 1 received edoxaban 60 mg daily plus clopidogrel. Patients with a CrCl of 15–50 mL/minute/1.73 m2, with a weight of 60 kg or less, or receiving P-gp inhibitors received edoxaban 30 mg daily.
   b. Group 2 received adjusted-dose warfarin to an INR or 2.0–3.0 plus clopidogrel plus aspirin 100 mg once daily.
   c. The primary endpoint of major or CRNM bleeding was not significantly different between dual therapy and triple therapy (20.7% vs. 25.6%; p=0.1154)
   d. Although not designed to evaluate ischemic outcomes, the differences were not different between the groups (7% vs. 6%)

8. Role of DOACs in this setting
    a. Use of a DOAC over warfarin makes sense, given the lower bleeding with DOACs across trials.
    b. Current evidence using rivaroxaban 15 mg daily with clopidogrel, dabigatran 150 mg twice daily with clopidogrel (except in older adult patients), or apixaban 5 mg twice daily with clopidogrel is the best evidence to date for reducing the bleeding risk in these patients.
    c. No trials large enough to evaluate ischemic or thrombotic outcomes are planned and would likely take longer to complete than the patent life of the current DOACs.

Patient Case

Questions 1–4 pertain to the following case.

B.D. is a 73-year-old man (height 69 inches, weight 80 kg) with newly diagnosed NVAF. He also has a history of hypertension, dyslipidemia, stable ischemic heart disease, and systolic heart failure. His current medications include aspirin 81 mg daily, enalapril 10 mg daily, atorvastatin 80 mg daily, metoprolol succinate 200 mg daily, furosemide 40 mg daily, spironolactone 25 mg daily, and amlodipine 10 mg daily. His current heart rate is 72 beats/minute and blood pressure is 122/72 mm Hg. His laboratory values include potassium 4.9 mEq/L, stable SCr 1.9 mEq/L, and blood glucose 101 mg/dL.

1. Which best depicts B.D.'s CHA_2DS_2-VASc score?
    A. 2.
    B. 3.
    C. 4.
    D. 5.

2. Which statement is most accurate regarding DOAC therapy for reducing the risk of stroke in patients with NVAF?
    A. All of the DOACs significantly reduced ischemic stroke in the phase III trials compared with warfarin.
    B. All of the DOACs significantly reduced hemorrhagic stroke in the phase III trials compared with warfarin.
    C. Apixaban is more effective than rivaroxaban because apixaban was superior to warfarin in the ARISTOTLE trial and rivaroxaban was only noninferior to warfarin in the ROCKET-AF trial.
    D. Dabigatran was studied in the highest-risk patients across the phase III trials and should not be used in patients with a $CHADS_2$ score of less than 3.

3. Which is the most appropriate regimen for reducing B.D.'s risk of stroke?
    A. Dabigatran 75 mg twice daily.
    B. Rivaroxaban 20 mg once daily.
    C. Apixaban 5 mg twice daily.
    D. Edoxaban 60 mg once daily.

4. Six months later, B.D. needs to undergo percutaneous coronary intervention for management of his coronary artery disease. He has had no medication changes, and his vital signs and laboratory information remain consistent. Which is the best available evidence-based approach to his antithrombotic therapy?
    A. Rivaroxaban 10 mg daily, plus clopidogrel 75 mg daily.
    B. Apixaban 2.5 mg twice daily, plus clopidogrel 75 mg daily.
    C. Adjusted-dose warfarin to an INR of 2.0–3.0, plus aspirin 81 mg daily, plus clopidogrel 75 mg daily.
    D. Edoxaban 15 mg once daily, plus aspirin 81 mg daily, plus clopidogrel 75 mg daily.

II. ANTICOAGULATION IN VALVULAR DISEASE

A. Risk of Thromboembolism: Can be 20-fold higher for patients with valve disease than for patients without this disease

B. ACCP guidelines (2014) and ACC/AHA guidelines (2017) provide the best information on preventing thromboembolism in patients with valvular disease.

C. Bioprosthetic Heart Valves
   1. The first 3 months is the highest-risk period of thromboembolism after bioprosthetic heart valve implantation, especially with mitral valves.
   2. Bioprosthetic heart valves have a lower long-term risk of thromboembolism than do mechanical heart valves.
   3. Risk of thromboembolism is higher with mitral valves than with aortic valves because of the larger diameter and therefore slower flow of the mitral valve compared with the smaller diameter and faster flow of the aortic valve.
   4. Aortic bioprosthetic valve – Patients in normal sinus rhythm should receive aspirin 50–100 mg daily for the first 3 months after valve implantation (AHA/ACC and ACCP). Warfarin therapy adjusted to an INR of 2.0–3.0 for at least 3 months and for as long as 6 months in patients at low risk of bleeding is also an option (AHA/ACC).
   5. TAVR – Patients should receive aspirin 50–100 mg and clopidogrel for the first 6 months after the valve procedure. Alternative is warfarin to an INR of 2.0–3.0 for 3 months in patients at low risk of bleeding. Aspirin is indefinite (AHA/ACC). Because of the metal in the ring of these valves, they are not completely bioprosthetic. DOACs should not be used with these valves.
   6. Mitral bioprosthetic valve – Patients should receive warfarin therapy with a target INR of 2.0–3.0 for the first 3 months after valve implantation. Afterward, patients can be transitioned to aspirin (ACCP). Aspirin therapy should be used with the addition of warfarin with a target INR of 2.0–3.0 in patients at low risk of bleeding (ACC/AHA).

D. Mechanical Heart Valves
   1. Warfarin therapy should be used regardless of the valve position.
   2. Patients should be bridged with a prophylactic dose of UFH, therapeutic doses of low-molecular-weight heparin (LMWH), or a prophylactic dose of LMWH until a therapeutic INR can be achieved with warfarin therapy. These strategies have not been compared with each other in any trials.
   3. Aortic mechanical heart valve
      a. Patients should receive warfarin therapy with a target INR of 2.0–3.0 (AHA/ACC and ACCP).
      b. Patients with thrombotic risk factors (e.g., AF, prior thrombotic event, left ventricular dysfunction) could have a target INR of 2.5–3.5 (AHA/AHA).
      c. Patients at low risk of bleeding should also receive aspirin 50–100 mg daily.
      d. Patients receiving an On-X aortic valve with no thrombotic risk factors who are also receiving low-dose aspirin may use a lower target INR of 1.5–2.0. Studies continue to evaluate this lower INR target for other patients receiving mechanical aortic valves (AHA/ACC).
   4. Mitral mechanical heart valve (AHA/ACC and ACCP for all)
      a. Patients should receive warfarin therapy with a target INR of 2.5–3.5.
      b. Patients at low risk of bleeding should also receive aspirin 50–100 mg daily.
   5. Aortic and mitral heart valves – Patients should receive warfarin therapy with a target INR of 2.5–3.5 (AHA/ACC and ACCP).

Patient Case

Questions 5 and 6 pertain to the following case.

S.D. is a 62-year-old woman (height 65 inches, weight 80 kg) with a history of significant primary mitral regurgitation. Her echocardiogram reveals significant leaflet flaring that is not amendable to mitral valve repair. She also has a history of hypertension, dyslipidemia, and gout. Her current medications include lisinopril 10 mg daily, hydrochlorothiazide 25 mg daily, simvastatin 40 mg daily, and allopurinol 300 mg daily. Her heart rate is 68 beats/minute and blood pressure is 128/74 mm Hg. Her CrCl is 68 mL/minute/1.73 m^2. She is scheduled to undergo valve replacement surgery and will receive a mechanical mitral valve. You are discussing the anticoagulation postoperative plan with S.D.'s team.

5. Which is the optimal regimen for preventing thrombosis?
   A. Subcutaneous enoxaparin 80 mg every 12 hours until adjusted-dose warfarin achieves a goal INR of 2.5–3.5, plus aspirin 81 mg daily.
   B. Subcutaneous enoxaparin 40 mg daily until adjusted-dose warfarin to an INR goal of 2.0–3.0, plus aspirin 81 mg daily.
   C. Intravenous UFH 6400-unit bolus, followed by an infusion of 1440 units per hour until adjusted-dose warfarin achieves a goal INR of 2.0–3.0.
   D. Adjusted-dose warfarin to an INR goal of 2.5–3.5, plus aspirin 81 mg daily.

6. Which statement best describes thrombotic risk in patients with valve replacement surgery?
   A. Bioprosthetic valves carry a higher risk of thrombosis than mechanical valves.
   B. The highest risk of thrombosis with bioprosthetic valve placement is during the first year after surgery.
   C. All patients with rheumatic mitral valve disease should receive anticoagulant therapy.
   D. Valve replacement in the mitral position carries a higher risk of thrombosis than in the aortic position.

III. PREVENTION OF VENOUS THROMBOEMBOLISM

A. Risk of Developing VTE
   1. VTE consists of a DVT, a pulmonary embolism (PE), or both.
   2. Risk factors for developing VTE are listed in Box 5. Risk factors are cumulative.
      a. Not all risk factors carry equal risk; patients with certain risk factors such as orthopedic surgery, trauma, cancer, certain hypercoagulable states, and a previous VTE have the highest risk of developing VTE.
      b. Risks of VTE on the basis of different patient groups are listed in Table 9. These event rates have typically been determined by venography in clinical trials and do not reflect the rates of symptomatic DVT or PE.
   3. Risk stratification
      a. Low risk (DVT incidence of less than 10% without thromboprophylaxis)
         i. Minor surgery in patients younger than 40 with no additional risk factors
         ii. Medically ill patients who are fully mobile
      b. Moderate risk (DVT incidence 10%–40% without thromboprophylaxis)
         i. Most general, patients undergoing open gynecologic or urologic surgery
         ii. Medically ill patients, bed rest or sick

c. High risk (DVT incidence 40%–80% without thromboprophylaxis)
    i. Major surgery in patients older than 40 plus a prior VTE
    ii. Cancer
    iii. Hypercoagulable state
    iv. Hip or knee arthroplasty, hip fracture surgery
    v. Major trauma
    vi. Spinal cord injury

4. Regimens vary depending on patient risk and clinical trial results.
    a. Mechanical prophylaxis
        i. Includes elastic stocking (limited efficacy) and intermittent pneumatic compression
        ii. Intermittent pneumatic compression has to be on the patient for at least 18 hours/day to show efficacy.
        iii. Both types of mechanical prophylaxis are poorly tolerated by patients.
        iv. For patients at high risk of bleeding, such as immediately post-surgery, with intent to start pharmacologic prophylaxis once hemostasis has occurred.
        v. Also may be used in the highest-risk patients, such as those with spinal cord injury, in combination with pharmacologic prophylaxis
    b. Pharmacologic prophylaxis
        i. LMWH – Subcutaneous enoxaparin or dalteparin
        ii. UFH – Subcutaneously twice daily or three times daily
        iii. Fondaparinux subcutaneously 2.5 mg daily
        iv. Adjusted-dose warfarin – Only in orthopedic surgery
        v. DOACs – Dabigatran, rivaroxaban, and apixaban – in orthopedic surgery; betrixaban and rivaroxaban – for extended prophylaxis in the medically ill
        vi. Aspirin – Questionable data, but is listed as a possible agent in orthopedic surgery

Box 5. Risk Factors for Developing VTE

Age ≥ 40
Surgery (e.g., orthopedic, thoracic, abdominal, and genitourinary)
Trauma (e.g., fracture of the spine, pelvis, femur, or tibia; spinal cord injuries)
Hypercoagulable states (e.g., resistance to activated protein C [factor V Leiden], deficiencies in antithrombin, protein C or protein S, antiphospholipid antibodies
Central venous catheterization
Estrogen use or selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Previous VTE
Cancer and its treatment (e.g., pancreas, lung, ovary, testes, urinary tract, breast, stomach)
Immobility or lower-extremity paresis
Certain medical disease states/conditions (e.g., stroke, or paralysis, acute infection, chronic obstructive pulmonary disease, inflammatory bowel disease, nephrotic syndrome, varicose veins, heart failure, acute MI, pregnancy)
Smoking
Obesity

VTE = venous thromboembolism.

Table 9. VTE Risk in Different Hospitalized Patient Groups

Patient Group	DVT Prevalence Without Prophylaxis
Medically ill patients Heart failure Chronic obstructive pulmonary disease Infection	10%–20%
General surgery	15%–40%
Major gynecologic surgery	15%–40%
Major urologic surgery	15%–40%
Neurosurgery	15%–20%
Stroke	20%–50%
Major orthopedic surgery Total hip replacement surgery Hip fracture surgery Total knee replacement surgery	40%–60% 57% 60% 84%
Major trauma	40%–80%
Patients with spinal cord injury	60%–80%
Critical care patients	10%–80%

DVT = deep venous thrombosis.

B. Orthopedic Surgery
   1. Typically considered one of the highest-risk settings for developing VTE
      a. More than 50% of patients have a VTE event without prophylaxis.
      b. DVT rates are higher in knee surgery, and PE rates are higher in hip surgery.
   2. Prophylactic regimens are listed in Table 10.
   3. Practical issues
      a. UFH has consistently shown insufficient protection against VTE in patients undergoing orthopedic surgery and should therefore not be considered an acceptable alternative.
      b. Although aspirin has a recommendation from ACCP and the American Association of Orthopaedic Surgeons guidelines, the recommendation is based on limited data with several limitations.
      c. Patients placed on mechanical prophylaxis after surgery because of a high risk of bleeding should have their risk of bleeding consistently reassessed, with pharmacologic prophylaxis started as soon as the bleeding risk is decreased.
      d. Patients undergoing knee arthroscopy typically do not need VTE prophylaxis beyond early mobilization unless they have additional VTE risk factors or have a complicated procedure. In those cases, patients should receive VTE prophylaxis with an LMWH.
      e. Dalteparin has not been evaluated in a published prospective trial for VTE prophylaxis in knee replacement surgery.
      f. Dabigatran is available in the United States for VTE prevention in patients undergoing hip replacement surgery, but not knee replacement surgery. Dabigatran was inferior to enoxaparin 30 mg twice daily in patients undergoing knee replacement surgery.
      g. Rivaroxaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip replacement surgery and enoxaparin 40 mg once daily and enoxaparin 30 mg twice daily in knee replacement surgery. Although major bleeding was not significantly increased in these studies, the definition of major bleeding did not include surgical site bleeding (considered nonmajor bleeding).

h. Apixaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip and knee replacement surgery, with no significant increase in major bleeding. Apixaban was not noninferior to enoxaparin 30 mg twice daily in knee replacement surgery, though the event rates were similar (9.0% apixaban vs. 8.8% enoxaparin). Although there was no difference in major bleeding, the combination of major and CRNM was significantly reduced with apixaban.

i. Timing of initiation of VTE prophylaxis after surgery is an important and complicated issue. The risk of thromboembolic events begins immediately after surgery; therefore, VTE prophylaxis is generally more effective when started earlier rather than later. The challenge lies in that early VTE prophylaxis is also associated with increased bleeding compared with VTE prophylaxis started later.

j. VTE prophylaxis after elective spinal surgery can typically be initiated 12–24 hours postoperatively. Prophylaxis may need to be delayed if the surgical site remains open.

Table 10. VTE Prophylaxis in Orthopedic Surgery

Orthopedic Indication	Enoxaparin	Dalteparin	Fondaparinux	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Knee replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery	2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr[a]	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5	Insufficient evidence	10 mg once daily initiated 6–10 hr after surgery	2.5 mg twice daily, initiated 12–24 hr after surgery
Hip replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery OR 40 mg SC q24hr initiated 10–12 hr before surgery	2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr OR 5000 IU SC q24hr initiated the evening before surgery	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5	110 mg initiated 1–4 hr after surgery; then 220 mg once daily	10 mg once daily initiated 6–10 hr after surgery	2.5 mg twice daily, initiated 12–24 hr after surgery
Hip fracture surgery	30 mg SC q12hr initiated 12–24 hr after surgery[a]	Insufficient evidence	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 ± 0.5	Insufficient evidence	Insufficient evidence	Insufficient evidence
Spine surgery	Pharmacologic prophylaxis is generally not recommended unless patients have additional risk factors of advanced age, malignancy, neurologic deficit, previous VTE, or an anterior surgical approach. Because of the lack of clinical trials, pharmacologic prophylaxis recommendations are general and include SC UFH or LMWH						

[a]Not approved by the U.S. Food and Drug Administration (FDA).

q = every; SC = subcutaneous(ly).

C. Non-orthopedic Surgery
   1. Contains a very heterogeneous group of patients and surgical procedures with varying risk
   2. Prophylactic regimens are listed in Table 11.
   3. Practical issues
      a. General surgery
         i. Meta-analysis comparisons between UFH and LMWHs show comparative efficacy in preventing DVT, but a greater reduction in the incidence of PE when an LMWH is used.
         ii. Mechanical prophylaxis is sometimes inappropriately selected over pharmacologic prophylaxis because of concerns for bleeding in surgical patients. A meta-analysis of almost 34,000 surgical patients showed that the most common bleeding complications are injection-site bruising (6.9%) and wound hematomas (5.7%). Major bleeding complications occur in less than 1% of patients.
      b. Neurosurgery
         i. Pharmacologic prophylaxis is typically given with mechanical prophylaxis, and the combination is as safe as, and more effective than, mechanical prophylaxis alone.
         ii. Pharmacologic prophylaxis is typically started 18–24 hours after neurosurgery.
      c. Vascular surgery
         i. Routine prophylaxis is recommended for patients with additional risk factors such as advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma.
         ii. Because of the limited number of trials of patients undergoing vascular surgery, dosing recommendations are based on evidence for pharmacologic agents in general surgery.
      d. Gynecologic surgery
         i. Low-risk gynecologic surgery procedures (laparoscopic procedures or procedures lasting less than 30 minutes) do not require prophylaxis beyond early ambulation.
         ii. Those undergoing major surgery without malignancy should receive UFH or an LMWH.
      e. Gynecologic cancer surgery
         i. UFH three times daily is more effective than twice daily. UFH three times daily and an LMWH seem to have similar efficacy and safety.
         ii. In a subgroup analysis of a general surgery trial, fondaparinux was more effective than dalteparin in patients undergoing surgery for cancer.
      f. Urologic surgery
         i. Patients undergoing a transurethral or laparoscopic urologic procedure do not require prophylaxis beyond early ambulation.
         ii. Because of the limited number of trials of patients undergoing urologic surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery.
      g. Bariatric surgery – Higher doses of LMWH and UFH are recommended. UFH 7500 units three times daily and enoxaparin 40 mg twice daily have been evaluated. Dalteparin 7500 units daily has been evaluated in a retrospective study using anti-factor Xa (anti-Xa) concentrations.
      h. Thoracic surgery – Because of the limited number of trials in patients undergoing thoracic surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery.
      i. Coronary bypass surgery
         i. Because of the limited number of trials of patients undergoing coronary artery bypass surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery.
         ii. Because of concerns about the higher incidence of heparin-induced thrombocytopenia in patients undergoing cardiac surgery, an LMWH may be preferred to UFH for prophylaxis.

Table 11. VTE Prophylaxis in Non-orthopedic Surgery

Surgical Indication	Unfractionated Heparin	Enoxaparin	Dalteparin	Fondaparinux
General surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Neurosurgery	5000 units SC q8hr	40 mg SC q24hr	Insufficient evidence	Insufficient evidence
Vascular surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Gynecologic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Urologic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Laparoscopic	Patients undergoing laparoscopic procedures without additional VTE risk factors do not require prophylaxis beyond early ambulation			
Bariatric	5000 units SC q8hr	40 mg SC q12hr	7500 IU SC q24hr	5 mg SC q24hr
Thoracic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Coronary bypass surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	Not discussed in current guidelines

D. Medically Ill Patients
   1. A heterogeneous group of hospitalized nonsurgical patients
   2. Clinical trials typically include patients with heart failure, acute infection, respiratory failure, inflammatory bowel disease, and rheumatoid arthritis and sometimes patients with cancer.
   3. Risk of VTE is typically lower than in surgical patients, but medically ill patients make up around 60% of all VTE cases because of the higher number of medically ill patients.
   4. Prophylactic regimens are listed in Table 12.
   5. Practical issues
      a. Many clinical trials have not shown efficacy with UFH 5000 units every 12 hours; therefore, UFH 5000 units every 8 hours may be the preferred UFH regimen.
      b. Although not evidence based, UFH 5000 units every 12 hours or enoxaparin 30 mg every 24 hours may be considered in individuals of advanced age and low weight (i.e., total body weight less than 50 kg) or with elevated baseline activated partial thromboplastin time [aPTT] (greater than 1.3–1.4 times baseline).
      c. Enoxaparin 20 mg once daily has been evaluated and is no more effective than placebo.
      d. Enoxaparin 20 mg once daily is equal in efficacy to UFH 5000 units every 12 hours.
      e. In head-to-head trials of UFH 5000 units every 8 hours and enoxaparin 40 mg daily, the regimens have had similar efficacy, except for in higher-risk medically ill patients (heart failure and ischemic stroke), in which enoxaparin seems to confer greater protection against VTE. In the same trials, enoxaparin has caused significantly less hematoma (greater than 5 cm) than UFH. Although some data suggest a lower bleeding rate with LMWH in medically ill patients, these findings are not consistent across trials.

Table 12. VTE Prophylaxis in Medically Ill Patients

UFH	Enoxaparin	Dalteparin	Fondaparinux	Rivaroxaban
5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr[a]	10 mg orally q24hr

[a]Not FDA approved.

6. Extended prophylaxis
    a. Risk of VTE is known to extend beyond discharge, with almost two-thirds of all events occurring within 30 days after hospitalization.
    b. Extended prophylaxis (35–42 days) with enoxaparin has shown a significant reduction in developing VTE, but with significantly more major bleeding than with enoxaparin for 10 days.
    c. Extended prophylaxis with apixaban 2.5 mg twice daily did not improve efficacy compared with enoxaparin for 10 days but did significantly increase major bleeding. This may be because of the lower-risk patients in this study, but further study is needed before apixaban is used in medically ill patients..
    d. Rivaroxaban is approved for extended VTE prophylaxis (35 +/- 4 days) in medically ill patients with moderate to severe restricted mobidity.
        i. Rivaroxaban 10 mg once daily significantly reduced VTE events without significantly increasing major bleeding compared to enoxaparin for 10 days in a subpopulation of the MEGELLAN trial
        ii. The original trial (n=8101) demonstrated a significant reduction in VTE events, but had significantly more major bleeding
        iii. Five groups found to have the highest risk of bleeding were removed from the data. These groups were as follows: treatment of active cancer during admission, use of dual antiplatelet therapy, history of bronchiectasis/pulmonary cavitation, active GI bleeding, or any bleeding in the previous 3 months. These patients comprised about 20% of the initial study population.
        iv. In the subpopulation (n=6447), VTE events were significantly reduced with rivaroxaban compared to enoxaparin/placebo, and major bleeding was not significantly increased.
        v. Elimination of these five groups was prospectively studied in the MARINER trial, in which major bleeding was similar to placebo for extended VTE prophylaxis.

E. Critically Ill Patients
    1. A group of patients at very high risk of developing VTE
    2. Typically includes patients in general critical care environments, including patients with trauma, acute spinal cord injury, and burns
    3. Prophylactic regimens are listed in Table 13.
    4. Practical issues
        a. Trauma
            i. A meta-analysis showed UFH to be no more effective than control.
            ii. Enoxaparin 30 mg twice daily has better efficacy than UFH 5000 units twice daily.
            iii. Observational analysis in 18,010 trauma patients showed a significant reduction in VTE events and death in patients receiving enoxaparin 30 mg twice daily compared with UFH 5000 units three times daily.
            iv. Evidence for dalteparin is based on observational data.
            v. Pharmacologic prophylaxis can safely be started within 24–36 hours. Pharmacologic prophylaxis for patients with acute spinal cord injury may need to be delayed for 48–72 hours.

vi. Patients with severe trauma (injury severity score greater than 23) may present with antithrombin deficiency; therefore, subcutaneous prophylaxis may be insufficient. Although not prospectively evaluated, an option may be to use an UFH infusion while the patient is in the intensive care unit early in the course of therapy. Only a slight increase in the aPTT (35–45 seconds) would be targeted because VTE prevention is the goal.

b. Acute spinal cord injury
   i. UFH three times daily had DVT and bleeding rates similar to enoxaparin twice daily, but PE was significantly reduced with enoxaparin.
   ii. Although enoxaparin 30 mg twice daily should be used during the acute injury period (about 2–3 weeks), either regimen can be used during the rehabilitation period.
   iii. In a retrospective case-control study, dalteparin 5000 units daily failed to show noninferiority to enoxaparin 30 mg twice daily in preventing VTE (9.7% vs. 1.6%). Further investigations of dalteparin are warranted.

c. Burns – The current evidence in burn patients comes from only observational studies with UFH, enoxaparin, and dalteparin. The most commonly used regimen is UFH 5000 units subcutaneously every 12 hours.

d. Critical care
   i. In medically ill or postoperative general surgery patients, UFH or LMWH can be used. In orthopedic surgery or trauma, an LMWH is preferred.
   ii. If mechanical prophylaxis is selected because of a patient's high risk of bleeding, the patient should be reevaluated often and changed to pharmacologic prophylaxis when the bleeding risk decreases.
   iii. Some pharmacodynamic studies suggest that critical care patients with significant edema or critical care patients receiving vasopressors will not achieve detectable anti-Xa concentrations with LMWH.
   iv. In the largest trial of VTE prevention in critical care patients, dalteparin 5000 units subcutaneously once daily provided similar protection against proximal DVT and better protection against PE, similar bleeding, and less heparin-induced thrombocytopenia than UFH 5000 units twice daily.
   v. Dalteparin does not have significant accumulation in critical care patients with renal insufficiency.
   vi. A retrievable inferior vena cava filter may be considered for PE prophylaxis, but this practice has limited evidence and is controversial.

Table 13. VTE Prophylaxis in Critically Ill Patients

Critical Care Setting	UFH	LMWH	Fondaparinux
Trauma	Insufficient evidence	Dalteparin 5000 IU SC q24hr Enoxaparin 30 mg SC q12hr	Insufficient evidence
Acute spinal cord injury	5000 units SC q8hr	Enoxaparin 30 mg SC q12hr or Enoxaparin 40 mg SC q24hr	Insufficient evidence
Burns	5000 units SC q8hr or 5000 units SC q12hr	Dalteparin 5000 IU SC q24hr Enoxaparin 40 mg SC q24hr	Insufficient evidence
Critical care	5000 units SC q8hr or 5000 units SC q12hr	Dalteparin 5000 IU SC q24hr Enoxaparin 30 mg SC q12hr or Enoxaparin 40 mg SC q24hr	Insufficient evidence 2.5 mg SC daily may be an option in suspected HIT

HIT = heparin-induced thrombocytopenia.

F. Duration of VTE Prophylaxis: Varies depending on patient risk and group (Table 15)

Table 14. Duration of VTE Prophylaxis

Indication	Duration
General medically ill patients	• 6–14 days or as long as immobile during acute illness • Rivaroxaban for patients with moderate to severe immobility for a total of 31–39 days (inpatient and outpatient)
Major general surgery	• Until hospital discharge
Major general surgery in patients with previous VTE	• Beyond hospital discharge for up to 28 days
Surgery for gastrointestinal, GU, or gynecologic cancer	• Beyond hospital discharge for up to 28 days
Total knee replacement surgery	• At least 10 days
Total hip replacement surgery	• 4–6 wk
Hip fracture surgery	• 4–6 wk
Critical care patients	• For the duration of the intensive care unit stay with reevaluation when the patient is transferred to the general medical ward
Major trauma	• Until hospital discharge and continued prophylaxis in patients with impaired mobility who undergo inpatient rehabilitation (up to 8 wk)
Patients with spinal cord injury	• Until hospital discharge in patients with incomplete injuries • For 8 wk in patients with uncomplicated complete motor injury • For 12 wk or until discharge from rehabilitation in patients with complete motor injury and other risk factors

GU = genitourinary.

Patient Case

7. B.G. is a 62-year-old man (height 69 inches, weight 110 kg) hospitalized for a heart failure exacerbation. He has symptoms when doing only limited exertion and has been out of bed only to use the bathroom for the past 3 days. His medical history also includes stable ischemic heart disease, hypertension, type 2 diabetes, and a PE 2 years ago. He currently smokes 2 packs/day and drinks 1 glass of wine with dinner most evenings. His current medications include bisoprolol 5 mg daily, lisinopril 10 mg daily, aspirin 81 mg daily, ranolazine 1000 mg twice daily, furosemide 40 mg daily, spironolactone 25 mg daily, and metformin 850 mg twice daily. His blood pressure today is 110/70 mm Hg and heart rate is 58 beats/minute. His laboratory values are normal except for a brain natriuretic peptide of 1498 ng/mL. Which is the most appropriate VTE prevention strategy for B.G.?

   A. Give fondaparinux 5 mg subcutaneously daily.

   B. Give apixaban 2.5 mg orally twice daily.

   C. Give enoxaparin 40 mg subcutaneously daily.

   D. B.G.'s risk does not warrant prophylactic therapy.

A. Special Populations – Information on use of VTE prophylaxis in special populations is in Box 6.

Box 6. Use of VTE Prophylaxis in Special Populations

Severe Renal Insufficiency
• Patients with renal insufficiency are at higher risk of bleeding, regardless of the anticoagulant used
• Patients with SCr > 2.5 mg/dL have been excluded from most clinical trials
• Enoxaparin should be dosed at 30 mg SC once daily, regardless of the indication for CrCl < 30 mL/min/1.73 m^2
• Dalteparin does not seem to significantly accumulate in patients with severe renal insufficiency until the CrCl is < 20 mL/min/1.73 m^2 when prophylactic doses are used
• Fondaparinux, rivaroxaban, and dabigatran are contraindicated in patients with a CrCl < 30 mL/min/1.73 m^2 and apixaban in patients with a CrCl < 25 mL/min/1.73 m^2
• Patients on hemodialysis (renal failure) should receive SC UFH
Obesity
• ACCP guidelines recommend possible weight-adjusted dosing in patients with obesity but provide no insight regarding at what weight this should be considered or what the "adjusted" dosing should be. Patients with obesity are at considerable risk of PE, but data from clinical trials on drug dosing are limited
• Several studies suggest that the typical LMWH dose has to be higher in patients with a BMI ≥ 40 kg/m^2
• Enoxaparin 40 mg SC twice daily has been more efficacious than 30 mg SC twice daily in patients undergoing bariatric surgery
• It is reasonable to use enoxaparin 40 mg twice daily or UFH 7500 units three times daily in patients with a BMI > 40 kg/m^2 or weight > 120 kg
• Injections of enoxaparin into the thigh in patients with obesity have a lower bioavailability than injections into the abdomen
Pregnancy
• Warfarin has been associated with congenital abnormalities when used during the first trimester and is therefore contraindicated. Although warfarin could be used during the second trimester, it is typically avoided throughout pregnancy
• A LMWH or UFH can be used throughout pregnancy
• LMWHs (or fondaparinux) are not contraindicated in the third trimester of pregnancy and can be used in the early third trimester. During the peripartum period, many prefer to use UFH because of its shorter half-life and risk of bleeding during delivery
• DOACs currently have no role in pregnancy

DOAC = direct-acting anticoagulant; PE = pulmonary embolism; SC = subcutaneous(ly).

IV. TREATMENT OF VENOUS THROMBOEMBOLISM

A. Introduction
   1. Around 2 million symptomatic and asymptomatic cases of VTE occur in the United States each year.
      a. Around 600,000 cases of PE each year
      b. More than 100,000 deaths from PE each year in the United States
   2. Consequences of VTE
      a. 30%–50% will develop a recurrent VTE event in the following 5–10 years.
      b. Around 30% develop postthrombotic syndrome.
      c. After a DVT event, 20% of patients die within the following year.
      d. After a PE event, 40% of patients die within the following year.

B. Pathophysiology
   1. Venous thrombosis forms from the components of Virchow's triad, which are venous stasis, vascular damage, and/or an inherited or acquired hypercoagulable state.
   2. Virchow's triad components are broken down into a list of risk factors (Box 5). Risk factors are cumulative, and some carry a higher risk than others (e.g., previous VTE, cancer, orthopedic surgery).
   3. Thrombus typically begins in the cusps of venous valves, where blood is more static. Vascular injury because of trauma or hypoxia initiates the clotting cascade with interaction between endothelial tissue factor and factor VII.
   4. An embolism from a DVT will lodge itself in the next available capillary bed, which is in the pulmonary vasculature, leading to PE.
   5. Despite therapy, areas of vascular damage may never fully recover, which leads to a continued risk of recurrent DVT events.
   6. Thrombosis often forms in and around venous valves, causing them to curl. Despite therapy, these valves may not recover their initial shape and function, which leads to continued venous stasis and continued risk of recurrent DVT and postthrombotic syndrome.
   7. Most upper-extremity DVTs are related to the use of central venous catheters.

C. Presentation and Assessment
   1. DVT
      a. Although many cases are asymptomatic, these acute asymptomatic DVTs can still have long-term complications.
      b. Most thrombi begin in the lower extremities.
      c. Superficial vein thrombosis typically does not embolize unless it extends into a deep vein, is at least 5 cm long, or is within 10 cm of the saphenofemoral junction.
      d. Proximal DVTs are more likely to embolize than are isolated calf DVTs.
      e. Signs and symptoms are nonspecific (Box 7) and need to be confirmed with the appropriate diagnostic test.
         i. D-dimer is a breakdown product of fibrin and fibrinogen and is typically elevated in the setting of VTE. Unfortunately, D-dimer is nonspecific and can also be elevated from conditions such as inflammation and infection. Therefore, a positive test does not tell the clinician whether it is VTE or something else. A negative test helps rule out thrombosis.
         ii. Venography is the gold standard diagnostic tool, but it is invasive (injecting dye into a vein in the heel/ankle), may be painful, and is rarely done in clinical practice.
         iii. Duplex ultrasonography is typically used in clinical practice. Although older Doppler ultrasonography could miss as many as 50% of small DVTs, the diagnostic methods available today are much improved because they include both visual and sound technology.
      f. DVT diagnosis
         i. Wells model can be used to determine the pretest probability of the patient's having a DVT (Table 15).
         ii. Patients with a low pretest probability who are younger than 65 and have a negative D-dimer can have DVT ruled out of their differential diagnosis.
         iii. Other patients should proceed to duplex ultrasonography or other imaging studies to confirm diagnosis.

Table 15. Wells Clinical Model for Evaluating the Pretest Probability of DVT[a,b]

Clinical Characteristics	Score
Active cancer (cancer treatment within previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for ≥ 3 days or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

[a]Clinical probability of DVT: low < 0; moderate 1–2; high > 3. In patients with symptoms in both legs, the more symptomatic leg is used.

[b]Calculator available at www.mdcalc.com/wells-criteria-for-dvt/.

Box 7. Clinical Presentation of DVT and PE

Deep Venous Thrombosis
Edema
Leg pain
Calf tenderness
Swelling
Discoloration (redness)
Increased leg warmth
Pulmonary Embolism
Tachycardia
Tachypnea
Hemoptysis
Dyspnea
Cough
Chest pain

2. PE (patients with hemodynamic stability [i.e., nonmassive])
    a. Similar to DVT cases, many PE cases are asymptomatic. Most thrombi begin in the lower extremities and embolize.
    b. Onset can be acute, with sudden death occurring in at least 10% of hospitalized cases before a diagnosis is confirmed.
    c. Signs and symptoms are nonspecific (Box 7) and need to be confirmed with the appropriate diagnostic test.
        i. D-dimer is similar to use with DVT. Serum concentrations are typically elevated in patients with PE. A negative test, combined with a low pretest probability score in patients younger than 65, can rule out PE.
        ii. CT is the most commonly used test for diagnosing PE. Unless it is unavailable, or a contraindication or concern exists with the use of contrast dye (e.g., renal dysfunction), this is the preferred diagnostic test for PE. Positive results have good specificity and generally confirm the diagnosis. Both the sensitivity and the specificity of the test are improved with central emboli over those that are more peripheral.
        iii. Ventilation/perfusion scanning measures the distribution of blood flow and airflow in the lungs. When there is a "mismatch" between blood flow and airflow in one area of the lung, the probability of PE is high. Specificity can be impaired in patients with heart failure, chronic obstructive pulmonary disease, or asthma. A scan with a negative finding has good specificity and generally rules out the diagnosis of PE. Findings reported as low or intermediate probability require additional diagnostic testing. This is the preferred diagnostic test for patients with renal dysfunction or with an allergy to contrast dye.
        iv. Pulmonary angiography is the gold standard diagnostic test for PE, but it is invasive, expensive, and associated with significant morbidity from the injection of contrast dye into the pulmonary artery.
    d. PE diagnosis
        i. The Wells model can be used to determine the pretest probability of the patient's having a PE (Table 16).
        ii. Patients who have a low pretest probability, who are younger than 65, and who have a negative D-dimer can have a PE ruled out of their differential diagnosis.
        iii. Other patients should proceed to CT or other imaging studies to confirm the diagnosis.

Table 16. Wells Criteria Clinical Model for Evaluating the Pretest Probability of PE[a,b]

Clinical Characteristic	Score
Cancer	1
Hemoptysis	1
Previous PE or DVT	1.5
Heart rate > 100 beats/min	1.5
Recent surgery or immobilization	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3

[a]Clinical probability of PE: low 0–1; moderate 2–6; high ≥ 7.

[b]Calculator available at www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/.

D. Acute Treatment of VTE
   1. Three different approaches to VTE treatment (Table 17)
   2. 2012 ACCP guidelines prefer DOACs to warfarin for patients with VTE without cancer because of less bleeding and greater convenience for patients and health care providers.
   3. Initiate therapy until the VTE is ruled out.

Table 17. Approaches to VTE Treatment

Treatment Strategy	Anticoagulant Choices
Bridging therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) initiated with warfarin and overlapped for at least 5 days and until a therapeutic INR is achieved. Then discontinue injectable anticoagulant and continue warfarin for the appropriate duration
Changing therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) for at least 5 days; then stop injectable anticoagulant therapy and initiate dabigatran or edoxaban for the appropriate duration
Monotherapy	Initiate rivaroxaban or apixaban at higher initial dose and then convert patient to lower maintenance dose for the appropriate duration

   4. Bridging therapy approach to VTE treatment
      a. Because of the delay in achieving systemic anticoagulation with warfarin therapy and the significant thrombus burden in patients with VTE, an injectable anticoagulant is initiated on the suggestion of a VTE and bridged to warfarin if the diagnosis is confirmed.
      b. Dosing of injectable anticoagulants for VTE treatment can be found in Table 18. Achieving therapeutic anticoagulation within the first 24 hours has been associated with reduced rates of recurrent VTE events.
      c. ACCP guidelines recommend initial injectable anticoagulant therapy with an LMWH or fondaparinux over intravenous or subcutaneous UFH.
      d. Warfarin dosing in the stable outpatient setting is similar to that discussed in the AF section. In the acute situation, dosing may depend on cofactors that drive initial dosing approaches.
      e. Goal INR is 2.0–3.0. Lower INR goals or 1.5–2.0 have not been proven as effective at preventing recurrent VTE and have not shown a meaningful safety benefit.
      f. Bridging to warfarin would likely be the preferred approach in the following:
         i. When patients have renal dysfunction because patients in the DOAC trials were excluded if their CrCl was less than 30 mL/minute/1.73 m^2 (less than 25 mL/minute/1.73 m^2 for apixaban)
         ii. When patients cannot afford DOAC therapy
         iii. When the transition to outpatient therapy makes acquiring a DOAC difficult. Pharmacists play a crucial role in assisting with confirming insurance coverage and other transition issues in these patients.

Table 18. Dosing of Injectable Anticoagulants for VTE

Agent and Route	Dosing
Unfractionated Heparin	
IV UFH[a]	Weight adjusted with an initial bolus of 80 units/kg, followed by an initial infusion of 18 units/kg/hr. Subsequent doses should be adjusted to maintain the institution's goal aPTT
SC UFH	17,500 units (250 units/kg) given q12hr.[b] Subsequent doses should be adjusted to maintain the institution's goal aPTT
SC UFH	333 units/kg, followed by 250 units/kg given q12hr without aPTT monitoring[c]
Low-Molecular-Weight Heparin (SC)	
Enoxaparin	1 mg/kg q12hr or 1.5 mg/kg q24hr[d]; if CrCl < 30 mL/min/1.73 m^2, give 1 mg/kg q24hr
Dalteparin[e,f]	100 units/kg q12hr or 200 units/kg q24hr
Pentasaccharide (SC)	
Fondaparinux	Weight < 50 kg – Give 5 mg q24hr Weight 50–100 kg – Give 7.5 mg q24hr Weight > 100 kg – Give 10 mg q24hr CrCl < 30 mL/min/1.73 m^2 – Contraindicated

[a]IV administration is preferred because of improved dosing precision.

[b]An initial 5000-unit IV bolus is recommended to achieve rapid anticoagulation.

[c]Good regimen for outpatient treatment for patients who cannot afford LMWH. Not practical for patients weighing > 80 kg because of issues with injection volume.

[d]1.5 mg/kg q24hr should be avoided in patients with current or history of malignancy, weight > 120 kg, DVT with iliac vein involvement, or antiphospholipid syndrome.

[e]No dosing recommendations for patients with severe renal insufficiency. Standard dosing likely not an issue until CrCl is < 20 mL/min/1.73 m^2.

[f]Not FDA approved for VTE treatment in patients without cancer, which may create insurance coverage issues.

aPTT = activated partial thromboplastin time.

5. Switching therapy approach in VTE treatment
    a. Dabigatran was evaluated in the RE-COVER I (n=2539) and II (n=2568) trials. Both trials had the same design, and both enrolled patients with a DVT (68%), a PE (23%), or both (9%).
        i. All patients received a median of 9 days of injectable anticoagulation. Patients randomized to dabigatran started the drug after discontinuing the injectable (Table 1; Table 19; Box 1). Patients randomized to warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were treated for 6 months.
        ii. In the combined trials (n=5107), the primary end points of symptomatic VTE events were similar between dabigatran and warfarin (2.4% vs. 2.2%; p=NS). Noninferiority was achieved (p<0.001).
        iii. Major bleeding was not significantly reduced with dabigatran (1.4% vs. 2.0%) overall.
        iv. Major and CRNM bleeding combined were significantly reduced with dabigatran compared with warfarin.
        v. Significantly more dyspepsia occurred with dabigatran than with warfarin.
    b. Edoxaban was evaluated in the Hokusai-VTE trial (n=8240), which included patients with a DVT (60%), a PE (30%), or both (10%).
        i. All patients received a median of 7 days of injectable anticoagulant. Patients randomized to edoxaban started the drug after discontinuing the injectable (Table 19; Box 4). Patients randomized to warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were followed for 12 months. The reduced edoxaban dose was used in 18% of patients with maintained efficacy and safety.

ii. The primary end point of symptomatic VTE events was similar between edoxaban and warfarin (3.2% vs. 3.5%; p=NS). Noninferiority was achieved (p<0.001).
iii. The patient subgroup enrolled with a severe PE, defined as producing right ventricular dysfunction (n=939), had a significant 48% reduction in the primary end point compared with warfarin.
iv. Major bleeding was not significantly reduced with edoxaban (1.4% vs. 1.6%) overall. When evaluating major bleeding only after starting oral study anticoagulant therapy, there was a relative 40% significant reduction with edoxaban.
v. Major and CRNM bleeding combined was significantly reduced with the use of edoxaban compared with warfarin.

6. Monotherapy approach in VTE treatment
   a. Rivaroxaban was evaluated in the EINSTEIN DVT (n=3449) and EINSTEIN PE (n=4832) trials. The trial designs were the same; however, they included different patient populations.
      i. Rivaroxaban was started without injectable therapy (Table 19) and was compared with enoxaparin 1 mg/kg every 12 hours bridged to dose-adjusted warfarin therapy (INR 2.0–3.0). Median duration of injectable anticoagulant was 8 days. Investigators determined whether patients would be treated for 3, 6, or 12 months. Only 12% and 5% of patients were treated for 3 months in the EINSTEIN DVT and PE trials, respectively.
      ii. Many patients in the rivaroxaban arms of EINSTEIN DVT (73%) and EINSTEIN PE (93%) still received injectable anticoagulation before enrolling in the study. These patients were transitioned to rivaroxaban on entering the trial (Box 2). Efficacy and safety outcomes did not differ if patients did or did not receive initial doses of injectable anticoagulation before receiving rivaroxaban.
      iii. In the combined trials (n=8282), the primary end point of symptomatic VTE events was similar between rivaroxaban and standard care (2.1% vs. 2.3%; p=0.41). Noninferiority was achieved (p<0.001).
      iv. Major bleeding was reduced by a relative 46% with the use of rivaroxaban compared with standard care (1% vs. 1.7%; p=0.002).
      v. Fragile patients (age older than 75, CrCl less than 50 mL/minute/1.73 m^2, or weight less than 50 kg) had a greater than 70% significant relative reduction in major bleeding, with each component of fragility reaching statistical significance independently.
      vi. Major and CRNM bleeding did not differ between the groups.
   b. Apixaban was evaluated in the AMPLIFY (n=5395) trial and included patients with a DVT (65%) or a PE (35%).
      i. Apixaban was started without injectable therapy (Table 19) and was compared with enoxaparin 1 mg/kg every 12 hours bridged to dose-adjusted warfarin therapy (INR 2.0–3.0). Median duration of injectable anticoagulant was 6.5 days. Patients were treated for 6 months.
      ii. 86% of patients in the apixaban arm initially received at least one dose of injectable anticoagulant before entering the study. These patients were transitioned to apixaban upon entering the trial (Box 3). Efficacy and safety outcomes did not differ if patients did or did not receive initial doses of injectable anticoagulation before receiving apixaban.
      iii. The primary end point of symptomatic VTE events was similar between apixaban and standard care (2.3% vs. 2.7%; p=NS). Noninferiority was achieved (p<0.001).
      iv. Major bleeding was reduced by a relative 70% with apixaban compared with standard care (0.6% vs. 1.8%; p<0.001).
      v. CRNM bleeding was also reduced with apixaban.

Table 19. DOAC Dosing in VTE

Agent	Standard Dosing	Dose Adjustment[a]	Avoid Use[a]
Dabigatran	150 mg twice daily after 5–10 days of injectable anticoagulation	None	• CrCl ≤ 30 mL/min/1.73 m^2 • Avoid use with CrCl 30–50 mL/min and concomitant use of P-gp inhibitors
Rivaroxaban	15 mg twice daily with food for 21 days, followed by 20 mg daily with food. After 6 mo, dose can be reduced to 10 mg daily. The 10-mg dose need not be given with food	None	• CrCl ≤ 15 mL/min/1.73 m^2 • Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily. After 6 months, dose can be reduced to 2.5 mg twice daily	50% dose reduction if receiving 5 or 10 mg twice daily with strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)	• SCr > 2.5 mg/dL • Strong CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) • If receiving 2.5 mg twice daily – Strong CYP3A4 and P-gp inhibitors (e.g., protease inhibitors, itraconazole, ketoconazole, conivaptan)
Edoxaban	60 mg once daily after 5–10 days of injectable anticoagulation	30 mg once daily • CrCl 15–50 mL/min/1.73 m^2 • Potent P-gp inhibitor (verapamil, dronedarone, or quinidine) • Weight ≤ 60 kg	• CrCl < 15 mL/min/1.73 m^2 • Rifampin

[a]CrCl in the DOAC trials was calculated using the Cockcroft-Gault equation with total body weight.

7. Outpatient therapy
   a. Around 80% of patients with a DVT can be treated on an outpatient basis.
   b. Most patients with a low-risk PE can also be treated at home. Use of outpatient treatment for PE may vary depending on geographic practices. Increased education is needed to promote this practice. The ability to use a DOAC without injectable anticoagulation offers an attractive option and easier transition of care. Rivaroxaban has been shown to be safe and effective using this approach in a small trial (HoT-PE) and significantly reduced resource use (MERCURY PE). Data with other DOACs are still developing.

E. Secondary Prevention of VTE
   1. All patients with VTE should be treated for at least 3 months (Table 20).
   2. Patients without a transient or reversible cause should be considered for long-term, potentially indefinite, oral anticoagulant therapy. Data analyses consistently show significant reductions in VTE with continued therapy for 12–24 additional months. Once therapy is discontinued, VTE rates catch up with those who did not receive extended therapy.

3. ACCP guidelines state that the oral anticoagulant need not be changed if therapy is continued beyond 3 months.
4. Options
    a. Adjusted-dose warfarin to an INR of 2.0–3.0
    b. Dabigatran 150 mg twice daily has been noninferior to warfarin for efficacy, with similar major bleeding but less major and CRNM bleeding (RE-MEDY trial). Dabigatran was superior to placebo for efficacy, with similar major bleeding but more major and CRNM bleeding (RE-SONATE trial).
    c. Rivaroxaban 20 mg daily was superior to placebo for efficacy, with similar major bleeding and more major and CRNM bleeding (EINSTEIN-Extension trial). Both rivaroxaban 20 mg and rivaroxaban 10 mg once daily were superior to aspirin, with similar safety (EINSTEIN CHOICE) in patients who had already completed 6 months of therapy (Table 19).
    d. Apixaban 5 mg and 2.5 mg twice daily were superior to placebo for efficacy, with similar safety (AMPLIFY-Extension) in patients who had already completed 6 months of therapy (Table 19).
    e. Edoxaban has not completed a long-term trial beyond the Hokusai-VTE trial.
    f. Aspirin (100 mg daily) has shown a 32% relative reduction in recurrent VTE events compared with placebo in two trials after patients completed at least 6 months of oral anticoagulant therapy. Relative reductions in patients receiving a DOAC compared with placebo are typically 70%–80%. The only study comparing a DOAC with aspirin is the EINSTEIN CHOICE trial, in which both rivaroxaban doses were superior to aspirin for efficacy, with similar low rates of bleeding.

Table 20. Duration of Anticoagulation Therapy in Patients with VTE

Indication	Therapy Duration	Comments
First episode of VTE secondary to a transient or reversible risk factor	3 mo	Recommendation applies to both proximal DVT and PE
First episode of unprovoked VTE	At least 3 mo	Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy Risk-benefit of indefinite therapy should be reassessed at periodic intervals
First episode of VTE with inherited or acquired thrombophilia[a]	At least 3 mo	Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy Several abnormalities or homozygous traits have at least additive risk Risk-benefit of indefinite therapy should be reassessed at periodic intervals
First episode of cancer-associated VTE	At least 3–6 mo and consider extended duration until cancer resolves and cancer treatment is completed	LMWH, rivaroxaban, or edoxaban are recommended over other anticoagulants
Second VTE (provoked or unprovoked)	Indefinite	Applies to patient not at high risk of bleeding

[a]Factor V Leiden; prothrombin G20210A; antiphospholipid antibody syndrome; excess factor VIII; deficiency in protein C, protein S, antithrombin deficiency.

F. Treatment of Cancer-Associated VTE
   1. Cancer is a significant risk factor for developing thrombosis.
      a. 15% of patients with cancer develop venous or arterial thrombosis.
      b. Cancer increases risk by up to 4-fold.
      c. Chemotherapy can increase risk by up to 6.5-fold.
      d. VTE is the second leading cause of death in most cancers.
      e. Risk differs by cancer type.
   2. LMWH is preferred as monotherapy for 3–6 months compared with warfarin therapy because of significantly improved efficacy without an increase in major bleeding.
      a. All LMWHs have evidence in these patients. Only dalteparin has specific FDA approval.
      b. The CLOT trial (n=676) used dalteparin 200 units/kg for the first 30 days, followed by 150 units/kg/day for 5 months, or warfarin for 6 months.
      c. Despite the evidence, many patients are not treated with LMWH because of cost or patient unwillingness to use injections for several months.
   3. The VTE treatment trials with DOACs enrolled 2.5%–6.0% of patients with active cancer. Compared with warfarin therapy, none of the DOACs had a significant or numerical increase in recurrent VTE events and had similar bleeding. Despite the low percentage of patients with active cancer enrolled in these trials, more than 1000 patients had active cancer. If patients are not going to receive an LMWH, the ACCP guidelines do not recommend warfarin over a DOAC in patients with cancer.
   4. Edoxaban and rivaroxaban have been compared with dalteparin in trials of patients with cancer-induced thrombosis. Collectively, these DOACs better reduced recurrent VTE, but with more major bleeding. Most of the excess bleeding occurs in patients with upper GI cancers.
   5. Data with apixaban for cancer-associated thrombosis treatment have now been published. Apixaban provided similar efficacy to dalteparin with similar major bleeding. The similar major bleeding in the overall trial is likely because of the lower enrollment of patients with upper gastrointestinal cancers.
   6. Although the ISTH and ASCO guidelines currently only recommend edoxaban and rivaroxaban for the treatment of cancer-associated VTE, the National Comprehensive Cancer Network has also included apixaban. It would seem prudent to still avoid the use of DOACs in the treatment of cancer-associated VTE in upper gastrointestinal cancers (esophageal or gastroesophageal).

Patient Case

8. R.S. is a 48-year-old man (height 70 inches, weight 90 kg) who presents to the emergency department with pain and swelling in his left leg. On examination, his leg is warm to the touch and tender and has 3+ pitting edema below the knee. His D-dimer is positive, and his duplex ultrasonography identifies a femoral-popliteal DVT. He understands that he will need to receive anticoagulant therapy but wants to avoid any injections, if possible. He has good insurance coverage. His other medical conditions are hypertension, HIV, and dyslipidemia. His medications include benazepril 20 mg daily, ritonavir 100 mg daily, darunavir 800 mg daily, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg daily, and atorvastatin 10 mg daily. His vital signs are stable, and his CrCl is 78 mL/minute/1.73 m^2. Which is the most appropriate anticoagulant regimen to initiate for R.S.?

   A. Rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg daily.

   B. Edoxaban 60 mg daily.

   C. Warfarin 2.5 mg daily.

   D. Apixaban 5 mg twice daily for 7 days, followed by 2.5 mg twice daily.

V. REVERSAL OF ANTICOAGULATION

A. Blood Products
   1. In the reversal of anticoagulant therapy, blood products are often part of the management of major bleeding.
   2. Whole blood is spun into red cells and platelet-rich plasma. The platelet-rich plasma is spun again to create platelets and plasma, and the plasma is frozen (FFP).
   3. Packed red blood cells (PRBCs)
      a. Not used for reversal but for management of bleeding to provide oxygen delivery to tissues
      b. 1 unit (around 250 mL) has a hematocrit of 70%–80% (twice whole blood) and can raise a patient's hemoglobin by 1–2 g/dL.
      c. Risks include transfusion reactions (e.g., chills, fever, urticaria, tachycardia), infection, and transfusion-related lung injury.
   4. Platelets
      a. May be used for reversal of antiplatelet therapy, but data are inconsistent
      b. Each unit (200–300 mL) contains 300,000–600,000 platelets per cubic millimeter.
      c. Same risk as with PRBCs
      d. Commonly part of a massive transfusion protocol
   5. FFP
      a. Cells have been spun out of blood, and the plasma contains the proteins in blood, mainly clotting factors.
      b. Must be frozen within 8 hours of blood collection and good for 12 months
      c. Commonly underdosed for reversing warfarin therapy – Takes multiple units (around 250 mL)
         i. Typical dose = 15–20 mL/kg (around 1.2–1.6 L)
         ii. Critically ill patients: 30 mL/kg (around 2.4 L)
      d. Requires type-and-crossing
      e. Takes 30–45 minutes to thaw
      f. Risk similar to risks with PRBCs and platelets
   6. Prothrombin complex concentrate (PCC)
      a. Clotting factor proteins are taken from a plasma sample.
      b. About 25-fold more concentrated in clotting factors than FFP
      c. Types (what each contains)
         i. 3-factor: Clotting factors II, IX, and X
         ii. 4-factor: Clotting factors II, IX, X, and VII (4PCC)
         iii. Activated PCC: II, IX, X, and VIIa
         iv. All contain varying concentrations of protein C, protein S, and UFH.
      d. Undergoes viral inactivation, reduces adverse effects, and does not require type-and-crossing
   7. Cryoprecipitate
      a. Derived by thawing a unit of FFP in the cold (cryo) (4°C) and then collecting the precipitated globulins, which are then resuspended in 20–40 mL of plasma
      b. Contains concentrations of factor VIII, XIII, von Willebrand factor, fibronectin, and fibrinogen
      c. May be used for bleeding from fibrinolytics to provide more fibrinogen to the patient. May be part of a massive transfusion protocol
      d. Dosing of cryoprecipitate can be calculated using the following formula: Number of bags to increase serum fibrinogen 1 g/dL = 0.2 × weight in kg
      e. Fibrinogen concentrate is also available (RiaSTAP).

8. Recombinant activated factor VII
    a. Not technically a blood product because made through recombinant technology
    b. Has been used to treat bleeding in patients receiving UFH, LMWH, and DOACs. Most trials are small and observational.
    c. Risk of thrombosis by giving an activated clotting factor
    d. Standard dose is 90 mcg/kg, but lower doses (e.g., 18–30 mcg/kg) have been documented to be effective and are significantly less expensive.
9. Massive transfusion protocols
    a. Indications – When to activate the protocol:
        i. 30%–40% blood volume loss with hypotension
        ii. 10 units of PRBCs in 24 hours
        iii. Transfuse entire blood volume in 24 hours
        iv. 50% blood volume replacement in 3 hours
        v. 4 units of PRBCs in 4 hours, knowing the need to give more
    b. Components – Typically, 1:1:1 of PRBCs, platelets, and FFP by volume
        i. Provides a hematocrit of 29%
        ii. Provides a platelet count of 88,000/mm^3
        iii. Provides clotting factor activity of 62% normal
        iv. May need to provide periodic units of cryoprecipitate
    c. Issues to monitor
        i. Dilution-induced thrombocytopenia
        ii. Citrate-induced hypocalcemia
        iii. Hyperkalemia
        iv. Acidosis

B. UFH
1. Protamine is an effective and rapid antidote for reversal of UFH.
    a. Basic protein derived from fish sperm that binds to heparin to form a stable salt
    b. Used to manage significant bleeding, reversal before surgery, or reversal of UFH given during surgery (e.g., coronary artery bypass grafting surgery)
    c. Dosing
        i. 1 mg of protamine neutralizes about 100 units of heparin.
        ii. In patients receiving an intravenous infusion of UFH, need to calculate the amount given in the past 3 hours. The total of the past hour, one-half the previous hour, and one-fourth for the hour before that. This assumes no bolus was given within the previous 8–12 hours.
        iii. Never administer more than 50 mg in a single dose outside going off cardiopulmonary bypass.
    d. aPTT can be used to assess the effectiveness of UFH neutralization.
    e. Adverse effects
        i. Hypotension, bradycardia
        ii. Minimized by giving over slow intravenous infusion instead of intravenous push
        iii. Patients previously receiving protamine sulfate–containing insulin, (i.e., NPH [neutral protein Hagedorn]) having undergone a vasectomy, or having a known sensitivity to fish are at an increased risk of having protamine antibodies and are more likely to have allergic reactions.
        iv. If risk of allergic reaction is of concern, corticosteroids and/or antihistamines can be given before protamine.
2. Blood products may be needed in patients with significant bleeding.

C. LMWH
   1. No specific antidote is available for LMWH.
   2. Protamine
      a. Reverses about 50%–60% of the anticoagulant activity of LMWH
      b. Dosing
         i. If dose of LMWH was given within 8 hours of need for reversal, give the following dose. One-half the initial dose can be repeated, if needed.
         ii. 1 mg of protamine neutralizes about 100 anti-Xa units of LMWH (dalteparin).
         iii. 1 mg of protamine neutralizes about 1 mg of enoxaparin (1 mg enoxaparin = 100 anti-Xa units).
         iv. If the LMWH dose was given more than 8 hours before the need for reversal, give 0.5 mg of protamine for every 100 anti-Xa units.
   3. Recombinant factor VIIa has been evaluated in small observational studies and found effective; it may be considered for significant bleeding when protamine fails.

D. Warfarin
   1. Vitamin K (phytonadione or vitamin K_1) – Reverses the anticoagulant effect of warfarin. Vitamin K comes into the vitamin K reduction cycle after vitamin K epoxide reductase converts vitamin K epoxide to vitamin K_1. Vitamin K_1 is then reduced to vitamin KH_2 by vitamin K reductase. Because the anticoagulant effect of warfarin is mainly because of the inhibition of vitamin K epoxide reductase, exogenous vitamin K can continue to be reduced and produce functional carboxylated clotting factors II, VII, IX, and X.
      a. Vitamin K reversal onset is delayed because several new clotting factors must be created to neutralize the effect of warfarin therapy.
         i. Oral vitamin K can take 24–48 hours to normalize the INR. This is the preferred route for managing INRs above the therapeutic range that is not associated with bleeding (Figure 1).
         ii. Intravenous vitamin K can take 8–12 hours to normalize the INR, with full effects not seen until 24 hours. Should be given as slow infusion instead of intravenous "push" because of concerns for allergic reactions
         iii. Subcutaneous vitamin K should be avoided because of delayed and erratic absorption in administering a fat-soluble vitamin into subcutaneous fat tissue.
      b. Vitamin K helps reverse high INRs (Figure 1) or helps when reversal is needed before planned surgical procedures.
      c. Of importance, vitamin K should not be overdosed because this can lead to overaggressive reversal and difficulty in reinitiating warfarin therapy (warfarin resistance).
   2. FFP vs. 4PCC – Historically, FFP has commonly been used for reversal of warfarin therapy in patients needing urgent surgery or when bleeding.
      a. 4PCC provides much faster reversal of the INR than does FFP.
         i. 4PCC typically only requires one dose (around 200 mL) compared with 4–12 units of FFP – Less time and less volume
         ii. 4PCC need not be thawed and has fewer adverse effects than a blood product.
      b. A study of patients with acute major bleeding receiving warfarin (n-202) compared FFP (INR 3.6) with 4PCC (INR 3.9).
         i. Patients receiving 4PCC had their INR reversed to baseline within 30 minutes; FFP took about 8 hours to achieve the same INR.
         ii. Patients receiving FFP had more fluid overload because of the volume administered than did patients receiving 4PCC (5.8% vs. 12.8%).
         iii. More posttreatment thrombotic events occurred with 4PCC than with FFP (8.7% vs. 5.5%).

c. Dosing – Only one 4PCC available in the United States. Dosing is based on actual body weight.
   i. INR 2 to less than 4: 25 units/kg with maximum dose of 2500 units
   ii. INR 4–6: 35 units/kg with maximum dose of 3500 units
   iii. INR greater than 6: 50 units/kg with maximum dose of 5000 units
   iv. Patients with an INR greater than 1.4 but less than 2.0 with cerebral bleeding may still receive 4PCC at a lower dose of 12.5–25 units/kg, but this approach was not part of the prospective study.

d. ACCP guidelines recommend a 4PCC over FFP for the rapid reversal of warfarin therapy.

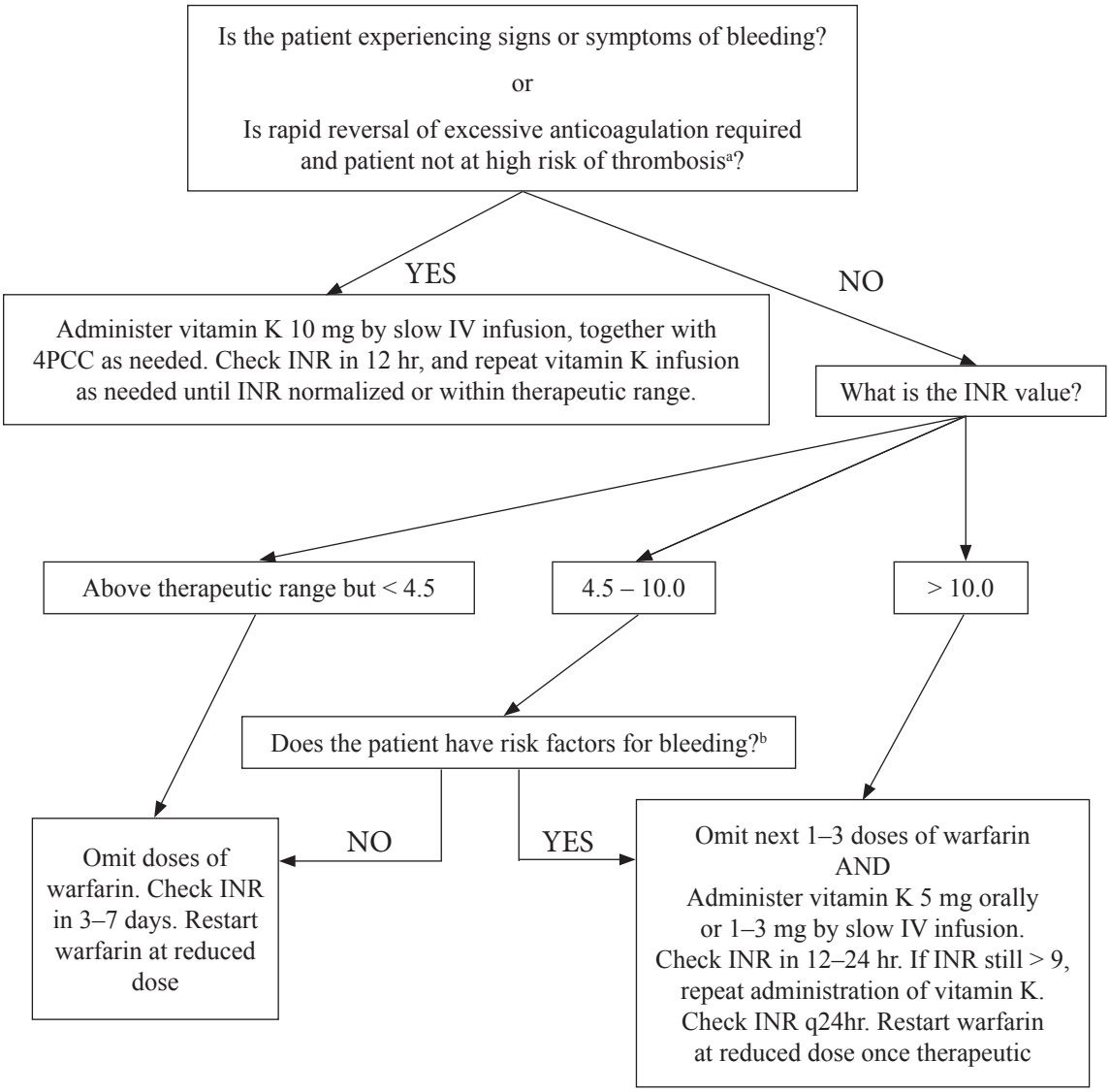
Is the patient experiencing signs or symptoms of bleeding?
or
Is rapid reversal of excessive anticoagulation required and patient not at high risk of thrombosis[a]?
YES
NO
Administer vitamin K 10 mg by slow IV infusion, together with 4PCC as needed. Check INR in 12 hr, and repeat vitamin K infusion as needed until INR normalized or within therapeutic range.
What is the INR value?
Above therapeutic range but < 4.5
4.5 – 10.0
> 10.0
Does the patient have risk factors for bleeding?[b]
NO
YES
Omit doses of warfarin. Check INR in 3–7 days. Restart warfarin at reduced dose
Omit next 1–3 doses of warfarin
AND
Administer vitamin K 5 mg orally or 1–3 mg by slow IV infusion. Check INR in 12–24 hr. If INR still > 9, repeat administration of vitamin K. Check INR q24hr. Restart warfarin at reduced dose once therapeutic

Figure 1. Management of bleeding and/or elevated INRs with warfarin therapy.

[a]History of hypercoagulability disorders, arterial or venous thrombosis within previous month, thromboembolism associated with malignancy, and high-risk mitral valve (with atrial fibrillation, poor ventricular function, or coexisting aortic valve).

[b]Age > 65, concurrent antiplatelet therapy, concurrent nonsteroidal anti-inflammatory drug use, history of gastrointestinal bleeding, recent surgery or trauma, high risk of fall or trauma, excessive alcohol use, renal failure, cerebrovascular disease, malignancy.

4PCC = 4-factor prothrombin complex concentrate; IV = intravenous(ly); q = every.

E. Dabigatran
   1. Reversal before most procedures is not necessary as long as the drug is held for the appropriate number of days (Table 21).
   2. Vitamin K and protamine are not effective. FFP cannot provide enough clotting factor replacement.
   3. Activated PCC at doses of 25–50 units/kg can normalize the aPTT, ecarin clotting time, and diluted thrombin time within 30 minutes. Lower doses may be effective but require further study.
   4. Recombinant factor VIIa and 4PCC have had mixed results and are typically reserved for when other agents fail to control bleeding in life-threatening settings.
   5. Idarucizumab – Specific antidote for dabigatran
      a. Fully humanized antibody Fab portion with a 350-fold affinity for dabigatran compared with thrombin. Can pull dabigatran out of circulation and off of thrombin and render it inactive
      b. REVERSE-AD trial (n=503) evaluated patients receiving dabigatran with uncontrolled bleeding (group A; n=301) or requiring urgent surgery (group B; n=202) receiving 5 g of idarucizumab.
         i. Primary outcome of the trial was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours of administering idarucizumab, as evaluated by the dilute thrombin time and the ecarin clotting time. The reversal was 100% in both groups for both assays. Full reversal occurred within 15 minutes and remained for 12–24 hours.
         ii. Group A most common sites of bleeding were gastrointestinal (46%), intracranial hemorrhage (33%), and trauma (26%). Cessation of bleeding in patients without intracranial hemorrhage was a median time of 2½ hours, with 68% having cessation within 24 hours.
         iii. Group B most common types of surgery were abdominal or infection (24%), fracture or septic arthritis (20%), and cardiovascular (18%). Periprocedural hemostasis was assessed by the investigators as normal in 93% of patients, mildly abnormal in 5%, and moderately abnormal in 2%, with no reports of severely abnormal hemostasis.
         iv. Thrombotic events occurred in 4.8% of patients within 30 days and 6.8% of patients within 90 days, most likely because patients were not reinitiated on anticoagulant therapy in a timely fashion.

F. Direct Xa Inhibitors
   1. Reversal before most procedures is not necessary as long as the drug is held for 1–2 days (Table 21). Holding for 4–5 days, as with warfarin, leaves the patient without anticoagulation and may increase the risk of thrombosis.
   2. Vitamin K and protamine are not effective. FFP cannot provide enough clotting factor replacement.
   3. Activated PCC at doses of 25–50 units/kg can normalize the prothrombin time within 30 minutes. Data are limited to animal models and spiked blood samples.
   4. PCC - Has been used for reversal of a direct Xa inhibitor. Doses are typically 50 units/kg, though some will give 25 units/kg and then re-dose if needed. Another option, with limited data, is to use a fixed dose of 2000 units as evaluated for warfarin reversal.
      a. Three small studies of healthy volunteers show a correction of the PT/INR, but none show a correction in anti-Xa activity.
      b. One prospective study (n=66) showed a 24-hour hemostatic efficacy of 85%. These patients were, on average, 18 hours from their last dose of factor Xa inhibitor. There was no assessment of anti-Xa function in these patients.
      c. Another prospective study (n=77) showed a 24-hour hemostatic efficacy of 69%. Although the average time from the last dose was 12 hours, anti-Xa function was not assessed.
      d. Not enough patients have been evaluated to determine the thrombotic potential. Administration of supratherapeutic concentrations of clotting factors in patients who already require anticoagulant therapy suggests a risk exists.

5. Andexanet alfa
    a. Decoy factor Xa protein with high affinity for Xa inhibitors (also LMWH and fondaparinux)
        i. Change in serine to alanine prevents catalytic activity and prevents the ability to convert prothrombin to thrombin.
        ii. GAL domain is also removed. This prevents the ability to bind to a phospholipid membrane (platelets) and incorporation of the decoy protein into the prothrombinase complex.
    b. Given as bolus and continuous 2-hour infusion. Within minutes of the bolus, Xa concentrations return to baseline, where they remain throughout the rest of the infusion. Although anti-Xa activity returns to placebo concentrations within 2 hours once the infusion is discontinued, thrombin generation is maintained. The concept is to provide a time window in which the bleed can be located and treated.
    c. In the ANNEXA-4 trial, andexanet reversed the anti-Xa activity of apixaban and rivaroxaban by 92% and provided hemostatic efficacy of 82% within 12 hours.
    d. The thrombotic event rate at the end of the ANNEXA-4 trial was 10% at 30 days. Only 2% of patients receiving any anticoagulant developed a thrombotic event, and none of the patients receiving oral anticoagulation developed a thrombotic event.
    e. Standard dose is a 400-mg intravenous bolus, followed by 4 mg/minute for 2 hours. Indicated for patients with last dose of apixaban of 5 mg or less, rivaroxaban dose 10 mg or less, or any dose of apixaban or rivaroxaban taken more than 8 hours earlier
    f. High dose is an 800-mg intravenous bolus, followed by 8 mg/minute for 2 hours. Indicated for patients with last dose of apixaban of 10 mg or rivaroxaban doses of 15 mg or 20 mg taken within the past 8 hours
    g. Not currently indicated for reversal of edoxaban, enoxaparin, or fondaparinux. In addition, only indicated for life-threatening bleeding, and not for patients requiring urgent surgery

Table 21. Preoperative DOAC Management

Drug	Preprocedural Holding Time
Dabigatran	
CrCl > 50 mL/min/1.73 m^2	1–2 days[a]
CrCl 15–50 mL/min/1.73 m^2	3–5 days[a]
Apixaban, rivaroxaban, and edoxaban	
Minor procedures	1 day
Minor procedures with CrCl < 30 mL/min/1.73 m^2	2 days
Major vascular procedures	2 days
Major vascular procedures with CrCl < 30 mL/min	3–4 days

[a]Consider longer times for patients undergoing major surgery, spinal puncture, or placement of spinal or epidural catheter or port.

Patient Case

9. K.D. is a 49-year-old man (height 68 inches, weight 100 kg) who was given a diagnosis of an idiopathic DVT 3 weeks ago. He currently takes warfarin 8 mg daily. He missed his INR readings last week when he went on a short vacation. Today, his INR is 10.4. He is not currently bleeding and has no risk factors for bleeding. In addition to holding his warfarin dose, which is the best initial strategy for managing K.D.'s high INR?

   A. Give vitamin K 2.5 mg orally.

   B. Give 4PCC 50 units/kg.

   C. Give vitamin K 5 mg orally.

   D. Give vitamin K 10 mg intravenously.

10. J.W. is a 58-year-old man receiving enoxaparin 40 mg subcutaneously daily for VTE prophylaxis. While trying to shave himself at 6 p.m., he cuts his neck, and the medical team cannot stop the bleeding. His last enoxaparin dose was given at 8 a.m. Which would be the most appropriate protamine dose for J.W.?

   A. 10 mg.

   B. 20 mg.

   C. 40 mg.

   D. 50 mg.

REFERENCES

Stroke Prevention in NVAF

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
2. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.
3. Dobesh PP, Fanikos J. Reducing the risk of stroke in patients with nonvalvular atrial fibrillation with direct oral anticoagulants: is one of these not like the others? JAFIB 2016;9:66-74.
4. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
5. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke inpatient who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
7. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1-76.
8. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 2019;74:104-32.
9. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018;154:1121-1201.
10. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
11. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.

Anticoagulation in Valvular Disease

1. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update on the 2014 AHA/ACC guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol 2017;70:252-89.
2. Whitlock R, Sun JC, Fremes SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl):e576S-e600S.

Prevention of VTE

1. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl):e278S-e325S.
2. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl):e227S-277S.
3. Kahn SR, Lim W, Dunn AS, at al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl):e195S-e226S.
4. Spyropoulos AC, Lipardi C, Xu J, et al. Improved benefit risk profile of rivaroxaban in a subpopulation of the MAGELLAN study. Clin Appl Thromb Hemost 2019;25:1-9.

VTE Treatment

1. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
2. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.

3. Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
4. Dobesh PP, Fanikos J. New oral anticoagulants for the treatment of venous thromboembolism: understanding the differences and similarities. Drugs 2014;74:2015-32.
5. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-15.
6. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141: e419S-e-494S.
7. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52.
8. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16:1891-4.
9. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Cancer-associated venous thromboemolic disease. Version 2.2018 – August 27, 2018. Available at https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed September 9, 2020.
10. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013;11:21.
11. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72.
12. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.

Reversal of Anticoagulation

1. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e44S-e88S.
2. Baugh CW, Levine M, Cornutt D, et al. Anticoagulation reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel. Ann Emerg Med 2020;76:470-85.
3. Connolly SJ, Crowther JW, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019;380:1326-35.
4. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: current status and future potential. Arterioscler Thromb Vasc Biol 2015;35:1736-45.
5. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the Anticoagulation Forum. Am J Hematol 2019; 94:697-709.
6. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl):e24S-e43S.
7. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e152S-84S.
8. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. N Engl J Med 2017;377:431-41.
9. Shander A, Goodnough LT. Update on transfusion medicine. Pharmacotherapy 2007;27(9 pt 2): 57S-68S.
10. Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. J Thromb Thrombolysis 2015;39:395-402.
11. Tomaselli GT, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral

anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76:594-622.

12. Voils S. Pharmacologic interventions for the management of critical bleeding. Pharmacotherapy 2007;27(9 pt 2):69S-84S.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

This patient with NVAF has three risk factors for stroke, according to the CHA_2DS_2-VASc score: 1 point for being age 65–74 years (68 years old), 1 point for having hypertension, and 1 point for being female. Answer A is incorrect because she would have a score of 1 using the $CHADS_2$ score, which would be from her hypertension, but that scoring system does not give a point for age unless the patient is 75 or older and gives no point for being female. Her HAS-BLED score is 1 for age older than 65. Although Answer D has the correct CHA_2DS_2-VASc score, the HAS-BLED score is incorrect. Even though the patient has hypertension for HASBLED, the systolic blood pressure needs to be greater than 160 mm Hg for it to receive 1 point. Therefore, her score is only 1, not 2 as in Answer D. Answer C is also incorrect because it over-calculates both the CHA_2DS_2-VASc score and the HAS-BLED score. Because the patient's CHA_2DS_2-VASc score is 3 and HAS-BLED score is 1, Answer B is correct. This patient is a candidate for anticoagulant therapy on the basis of stroke risk and has an acceptable bleeding risk from warfarin therapy.

2. Answer: B

Given the patient's CHA_2DS_2-VASc score of 3 and no contraindications to anticoagulant therapy, she is at high risk of ischemic stroke and needs anticoagulant therapy, making Answer A incorrect. Apixaban would be an acceptable option, but the reduced dose of 2.5 mg twice daily is only for patients with two high-risk bleeding features (age 80 and older, weight 60 kg or less, or SCr 1.5 mg/dL or greater). She has one factor with a weight less than 60 kg (57 kg), but age (72 years) and SCr (0.8 mg/mL) do not meet the criteria. Therefore, she should receive apixaban 5 mg twice daily, making Answer C the incorrect apixaban dose. In contrast, edoxaban should have a dose reduction with a body weight of 60 kg or less. Answer D is incorrect because the correct edoxaban dose for this patient would be 60 mg daily. Rivaroxaban is only dose reduced when the CrCl is less than 50 mL/minute/1.73 m^2. Because this patient's renal function is above that level, Answer B is correct for using the correct dose of anticoagulant.

3. Answer: D

Answer A is incorrect; although protamine is an antidote for UFH and a partial antidote for LMWH, it would not be expected to reverse a direct Xa inhibitor. Answer B is incorrect because FFP does not provide enough clotting factors to reverse a direct Xa inhibitor. Idarucizumab is a fully humanized antibody to dabigatran and will bind dabigatran more strongly than thrombin. Idarucizumab is an effective reversal agent for dabigatran (Answer D is correct). Answer C is incorrect because andexanet alfa is a recombinant factor Xa that binds factor Xa inhibitors but has no impact on the direct thrombin inhibitor dabigatran.

4. Answer: A

Patients with a bioprosthetic mitral valve require dose-adjusted warfarin therapy to a target INR of 2.0–3.0, but patients with bioprosthetic aortic valves do not need anticoagulation. Moreover, the INR goal of 2.5–3.5 would be inappropriate for any bioprosthetic valve replacement. In addition, the initial warfarin dose is too high for a patient who is taking amiodarone and 70 years of age. A more appropriate starting dose would be 2 mg or 2.5 mg daily. Answer B is incorrect for many reasons. Neither DOAC would be used unless the patient had concomitant AF. Although data are limited, it is generally thought that patients with AF with bioprosthetic valves can receive therapy with a DOAC. This patient does not have AF and does not require anticoagulation for the valve, making Answers C and D incorrect. Answer A, low-dose aspirin, is all that is indicated because of the lower thrombogenic potential of an aortic valve compared with a mitral valve, and a bioprosthetic valve compared with a mechanical valve.

5. Answer: B

The correct duration of antithrombotic therapy is at least 3 months. This is the duration for both aortic and mitral bioprosthetic valves, making Answer B correct. Answer A is too short and might be confused with the duration of dual antiplatelet therapy in patients with a bare metal stent. Answer C is also incorrect and might be confused with the duration of dual antiplatelet therapy for patients receiving a drug-eluting stent. Answer D would be correct if the patient had received a mechanical heart valve, but his valve is bioprosthetic.

6. Answer: C
This patient has five risk factors for developing VTE, making Answer C correct. She is 40 years or older (51 years), has obesity (BMI 33 kg/m^2), recently had surgery, has immobility, and smokes, making Answers A, B, and D incorrect.

7. Answer: C
Answer B is incorrect because the duration of higher-intensity rivaroxaban should be 21 days, not 7 days. Apixaban's duration of higher-intensity therapy is 7 days. Answer D is incorrect because the UFH dosing is insufficient. This is the dosing in patients with an acute coronary syndrome. Patients receiving dabigatran or edoxaban must first receive at least 5 days of injectable therapy. The dosing of enoxaparin and the DOAC is correct in both Answers A and C, but the DOAC should not be overlapped with the injectable anticoagulant, making Answer A incorrect and Answer C correct.

8. Answer: C
Protamine 39 mg is the correct dose for this patient. To calculate the dose, add the amount of UFH given in the past hour (2250 units) plus one-half given in the previous hour (1125 units) plus one-fourth of what was given the hour before that (563 units). This gives a total of 3938 units of UFH in the past 3 hours. A dose of 1 mg of protamine for every 100 units of UFH equals a protamine dose of 39 mg (Answer C). Because the bolus dose was given more than 3 hours ago, it is not part of the calculation. Although 100 units would be the calculated dose according to the bolus, the bolus was given too long ago to be considered (Answer A), and no more than 50 mg is given at one time, making Answers A and B incorrect. The dose of 22.5 mg in Answer D is incorrect because this dose considered only the amount of UFH received in the past hour, not the past 3 hours.

9. Answer: C
Although dabigatran can be used for VTE prevention in patients with hip replacement surgery, it did not meet noninferiority and is therefore not indicated in patients with knee replacement surgery, making Answer A incorrect. Answer B is the correct enoxaparin dosing for hip replacement surgery, but the correct dose for knee replacement surgery is 30 mg twice daily, making Answer B incorrect. Edoxaban is not indicated for hip or knee replacement surgery in the United States. All studies with edoxaban were done only in Japan, making Answer D incorrect. Answer C is correct because this is the correct dosing of fondaparinux for hip and knee replacement surgery.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient's CHA_2DS_2-VASc score is 3. He receives 1 point for his age of 65–74 years (73 years), 1 point for hypertension, and 1 point for heart failure (Answer B). A score of 2 (Answer A) would be correct when using the $CHADS_2$ score instead of the CHA_2DS_2-VASc score because his age would not give him any points in the $CHADS_2$ score. The patient's history of stable ischemic heart disease may be assumed to be 1 point for vascular disease, but this is only 1 point in patients with a prior MI, peripheral arterial disease, or aortic disease, making Answer C incorrect. Given his score of 3, Answer D would also be incorrect.

2. Answer: B

Critical evaluation of the DOAC phase III trials is necessary to dispel any misconceptions clinicians may have concerning the conclusions of these data. Only dabigatran significantly reduced ischemic stroke in the RE-LY trial, but this may be questioned by the lack of blinding in the trial, making Answer A incorrect. The benefit of the DOACs in each of their respective trials was a significant reduction in hemorrhagic stroke. This drove the overall benefit and safety for all of the agents (hemorrhagic stroke is counted as an efficacy and safety end point in all the trials), making Answer B correct. Although clinicians may reach the conclusions in Answer C, evidence is insufficient to make this claim. Cross-trial comparisons are inappropriate because of the different risks of patients studied and the different sample sizes of the trials. The 0.3% absolute difference in the ARISTOTLE and ROCKET-AF trials makes it difficult to conclude that one agent is more efficacious than the other without a head-to-head randomized controlled trial. Answer D is also incorrect because bleeding was similar to warfarin in the RE-LY trial with dabigatran and lower with edoxaban in the ENGAGE trial. Despite these data, the bleeding rates in the trials cannot be compared because of the different times in which bleeding events were accrued in the trials.

3. Answer: C

Given the patient's CHA_2DS_2-VASc score of 3, he at high risk of ischemic stroke and should receive anticoagulation. The patient's CrCl is about 40 mL/minute/1.73 m^2 using the Cockcroft-Gault equation with total body weight. Although any of these agents would be acceptable in this patient, not all of the dosing regimens are correct. The dabigatran dose should not be reduced from 150 mg twice daily to 75 mg twice daily until the CrCl is less than 30 mL/minute/1.73 m^2, making Answer A incorrect. Both rivaroxaban and edoxaban should be dose reduced when the CrCl is less than 50 mL/minute/1.73 m^2 in patients with NVAF. Rivaroxaban goes from 20 mg daily to 15 mg daily, and edoxaban goes from 60 mg daily to 30 mg daily, making Answers B and D incorrect. Apixaban is listed at the typical dose and is not reduced to 2.5 mg daily unless the patient meets two of three criteria (age 80 or older, weight 60 kg or less, or SCr 1.5 mg/dL or greater). This patient has the elevated SCr, but his age and weight do not meet these criteria. Therefore, full-dose apixaban is correct (Answer C) for this patient.

4. Answer: A

Trials to date have mainly evaluated the safety of these regimens. However, efficacy trials are not planned, and decisions will have be based on the trials already completed. Although trials are being conducted with apixaban and edoxaban in the setting of AF and percutaneous coronary intervention, the results are not expected until 2019. Answer D would not be supported by the currently available evidence until dosing or safety data become available. Answer B would be incorrect because the apixaban dose evaluated in the AUGUSTUS trial was 5 mg twice daily. Answer A (rivaroxaban plus clopidogrel) and Answer C (warfarin, aspirin, and clopidogrel) were compared with each other in the PIONEER AF-PCI trial, with the rivaroxaban regimen significantly reducing clinically relevant bleeding. Because of better safety, Answer A is correct and Answer C is incorrect. The 10-mg dose of rivaroxaban is correct because the patient's CrCl is 40 mL/minute/1.73 m^2. In the trial, patients with a CrCl of 30–50 mL/minute/1.73 m^2 received rivaroxaban 10 mg daily instead of 15 mg daily.

5. Answer: A

Answer B would be correct if the patient were receiving a mechanical aortic valve replacement instead of a mechanical mitral valve. The difference is the target INR, which is higher for the mitral valve because of the

higher risk of thrombosis of the mitral position (larger valve with slower flow) than of the aortic position. Bridging therapy with an injectable anticoagulant is recommended, making Answer D incorrect. Bridging options include prophylactic UFH and prophylactic or therapeutic LMWH. Because Answer C includes therapeutic UFH, it would be incorrect. Answer C also has the incorrect INR goal and does not include aspirin. Answer A contains all of the correct components. Therapeutic LMWH is an acceptable option for bridging, the INR target of 2.5–3.5 is correct, and low-dose aspirin is added because the patient is not at high risk of bleeding.

6. Answer: D

Answer A is incorrect because mechanical valves have a higher risk of thrombosis than do bioprosthetic valves. This is shown in the higher INR goal, addition of aspirin, and longer therapy duration (regardless of valve position) for mechanical valves than for bioprosthetic valves. The highest risk of thrombosis with a bioprosthetic valve is during the first 3 months after valve placement, not out to 1 year, making Answer B incorrect. Answer C is also incorrect. Although most patients with rheumatic mitral disease do require anticoagulation, patients in normal sinus rhythm with a left atrial diameter less than 55 mm do not require any antithrombotic therapy. Answer D is correct. Because of the larger valve size and slower flow through the mitral valve than through the aortic valve, mitral valves carry a higher risk of thrombosis. This is shown by the more aggressive anticoagulant regimen, regardless of the type of valve used (bioprosthetic or mechanical).

7. Answer: C

This patient has several risk factors for VTE and requires prophylaxis, making Answer D incorrect. Although fondaparinux is effective and safe for VTE prophylaxis in medically ill patients, the appropriate dose is 2.5 mg subcutaneously daily, not 5 mg daily (Answer A). Although apixaban has been studied for VTE prophylaxis, it did not have efficacy and safety when evaluated for extended prophylaxis, making Answer B incorrect. Several studies have shown the efficacy and safety of enoxaparin 40 mg subcutaneously once daily for VTE prophylaxis in medically ill patients, making Answer C correct.

8. Answer: D

This patient can be treated for his DVT event without receiving injectable anticoagulation. Both rivaroxaban and apixaban provide this ability. Because edoxaban requires at least 5 days of injectable therapy before initiation and warfarin must be bridged with injectable anticoagulation for at least 5 days, both Answers B and C are incorrect. The rivaroxaban regimen in Answer A is the standard correct regimen, but the patient is taking a protease inhibitor. Protease inhibitors, especially ritonavir, are potent P-gp and CYP3A4 inhibitors and are contraindicated in use with rivaroxaban, making Answer A incorrect. Although the typical apixaban regimen for VTE treatment is 10 mg twice daily for 7 days, followed by 5 mg twice daily, patients receiving potent P-gp and CYP3A4 inhibitors can still use apixaban but at a 50% dose reduction, making Answer D correct.

9. Answer: C

Because this patient is not bleeding and rapid reversal is unnecessary, 4PCC is not needed, making Answer B incorrect. The lack of bleeding in this patient also makes high dose (10 mg) IV vitamin K uncesssary, making Answer D incorrect. For an INR over 10 with no bleeding, the dose of oral vitamin K is 5 mg, making Answer C correct and the dose of 2.5 mg (Answer A) incorrect.

10. Answer: B

Protamine is an acceptable approach to reversal of enoxaparin therapy because it reverses about 50%–60% of the anticoagulant effect of LMWH. One milligram of protamine will reverse 100 anti-Xa units of LMWH. One milligram of enoxaparin is equal to 100 anti-Xa units. Thus, 1 mg of protamine will reverse 1 mg of enoxaparin. Typically, a dose of 40 mg of protamine would be used to reverse a dose of 40 mg of enoxaparin. However, when the last dose of enoxaparin is more than 8 hours from the need for protamine, one-half the dose should be given. Therefore, a dose of 20 mg of protamine (Answer B is correct) is appropriate in this patient, not a dose of 40 mg (Answer C is incorrect). The dose of 10 mg is too low for this setting, making Answer A incorrect. Although 50 mg of protamine (Answer D) is the maximum dose to be given at one time, it is more than twice as much protamine as would be required in this patient setting and is incorrect.

Endocrine and Metabolic Disorders

Brian K. Irons, Pharm.D., FCCP, BCACP

Texas Tech University Health Sciences Center
Jerry H. Hodge School of Pharmacy
Lubbock, Texas

Endocrine and Metabolic Disorders

Brian K. Irons, Pharm.D., FCCP, BCACP

Texas Tech University Health Sciences Center
Jerry H. Hodge School of Pharmacy
Lubbock, Texas

Learning Objectives

1. Differentiate between the diagnostic and classification criteria for various endocrine and metabolic disorders, including type 1 and type 2 diabetes, diabetes insipidus, polycystic ovary syndrome, obesity, and disorders of the thyroid, adrenal, and pituitary glands.
2. Review the various therapeutic agents used in treating endocrine and metabolic disorders.
3. Select appropriate treatment and monitoring options for a given patient presenting with one of the previously mentioned endocrine or metabolic disorders.
4. Recommend appropriate therapeutic management for secondary complications from diabetes or thyroid disorders.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
A1C	Hemoglobin A1C
ACTH	Adrenocorticotropic hormone
ARB	Angiotensin receptor blocker
BG	Blood glucose
BMI	Body mass index
DI	Diabetes insipidus
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP	Dipeptidyl peptidase-4
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GH	Growth hormone
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
IGF-1	Insulin-like growth factor-1
LH	Luteinizing hormone
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
SGLT-2	Sodium glucose cotransporter-2
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TDI	Total daily insulin
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 66-year-old Hispanic man (weight 123.8 kg; body mass index [BMI] 42 kg/m^2) with a history of dyslipidemia and hypertension received a diagnosis of type 2 diabetes (T2D). After 1 month of exercise and dietary changes and no diabetes medications, his hemoglobin A1C (A1C) and fasting glucose concentration today are 11.5% and 362 mg/dL, respectively. Which set of drugs is best to initiate?
   A. Metformin and glipizide.
   B. Glipizide and insulin glulisine.
   C. Pioglitazone and acarbose.
   D. Insulin detemir and glulisine.

2. A patient weighing 65 kg with symptoms of hyperglycemia and a fasting glucose concentration of 298 mg/dL is given a diagnosis of type 1 diabetes (T1D). The patient's physician asks for a recommendation of an appropriate starting dose of basal insulin and estimates the total daily insulin (TDI) needs of 0.4 unit/kg/day. Which recommendation is most appropriate?
   A. 13 units of insulin detemir.
   B. 13 units of insulin aspart.
   C. 26 units of insulin glargine.
   D. 26 units of insulin glulisine.

3. A patient with T2D has a blood pressure reading of 152/84 mm Hg, a serum creatinine (SCr) of 1.8 mg/dL, and two recent random urine albumin/creatinine concentrations of 420 and 395 mg/g. Which class of drugs (barring any contraindications) is best to initiate in this patient?
   A. Thiazide diuretic.
   B. Dihydropyridine calcium channel blocker.
   C. Angiotensin receptor blocker (ARB).
   D. Non-dihydropyridine calcium channel blocker.

4. Regarding propylthiouracil and methimazole in the treatment of hyperthyroidism, which statement is most appropriate?

A. Propylthiouracil is clinically superior to methimazole in efficacy.

B. Propylthiouracil may be associated with greater liver toxicity than methimazole.

C. Both agents are equally efficacious in the treatment of Hashimoto disease.

D. Both medications should be administered three times daily.

5. Which medication is most appropriate for a patient with a diagnosis of Cushing syndrome who has had inadequate symptom relief after surgical resection for a pituitary adenoma?

A. Ketoconazole.

B. Spironolactone.

C. Hydrocortisone.

D. Bromocriptine.

6. A physician asks for a recommendation of initial therapy for a patient with T2D. The physician states that metformin is no longer an option for this patient. An A1C obtained today is 9.4% (personal goal 7%), and the patient's estimated glomerular filtration rate (eGFR) is 29 mL/minute/1.73 m^2. Which agent would be the best recommendation?

A. Canagliflozin.

B. Alogliptin.

C. Insulin glargine.

D. Exenatide.

7. A 76-year-old woman (weight 47 kg) recently given a diagnosis of Hashimoto disease presents with mild symptoms of lethargy, weight gain, and intolerance to cold. Her thyroid-stimulating hormone (TSH) is 12.2 mIU/L and free thyroxine (T_4) is below normal limits. She has a history of hypertension and underwent a coronary artery bypass surgery 2 years ago. Which would be the most appropriate initial treatment for this patient?

A. Levothyroxine 25 mcg once daily.

B. Levothyroxine 75 mcg once daily.

C. Liothyronine 25 mcg once daily.

D. Liothyronine 75 mcg once daily.

8. A woman with T2D has an A1C of 8.6%. She is receiving insulin glargine (60 units once daily at bedtime) and insulin aspart (8 units before breakfast, 7 units before lunch, and 12 units before dinner). She is consistent in her carbohydrate intake at each meal. Her morning fasting plasma glucose (FPG) and premeal blood glucose (BG) readings have consistently averaged 112 mg/dL. Her bedtime readings are averaging 185–200 mg/dL. Which is the best insulin adjustment to improve her overall glycemic control?

A. Increase prebreakfast aspart to 10 units.

B. Increase predinner aspart to 14 units.

C. Increase bedtime glargine to 65 units.

D. Increase prelunch aspart to 9 units.

9. A 53-year-old woman with a history of Graves disease had ablative therapy 3 years ago, after which she had significant symptom relief and became euthyroid. Her thyroid laboratory values today include TSH 0.12 mIU/L and free T_4 3.8 g/dL. She states that many of her previous symptoms have returned but are mild. Which would be the most appropriate treatment for her condition?

A. Methimazole.

B. Lugol's solution.

C. Propylthiouracil.

D. Metoprolol.

10. A 65-year-old man with T2D has received metformin 1000 mg twice daily for the past 2 years. His A1C today is 7.8%. His morning FPG readings are consistently at goal. His after-meal glucose readings average 190–200 mg/dL. Which would be most appropriate for this patient?

A. Increase metformin to 1000 mg three times daily.

B. Add insulin glargine 10 units once daily.

C. Change from metformin to insulin glargine 10 units once daily.

D. Add saxagliptin 5 mg once daily.

11. A 34-year-old woman has a BMI of 33 kg/m^2. With dietary changes, she has lost 0.9 kg (2 lb) in 6 months. She exercises regularly but cannot do more because she has two jobs and young children.

Her medical history is significant for depression, T2D, and substance abuse. Her current medications include metformin 1000 mg twice daily, insulin glargine 24 units once daily, and sertraline 100 mg once daily. Her A1C is well controlled, but she occasionally has hypoglycemic episodes. She is most concerned about weight loss. Which would be the best recommendation to help her lose weight?

A. Continue her diet and exercise routine; additional intervention is unwarranted.

B. Initiate liraglutide 3 mg once daily.

C. Initiate phentermine/topiramate 3.75/23 mg once daily.

D. Initiate orlistat 120 mg three times daily with meals.

12. A 53-year-old Hispanic woman has a BMI of 44 kg/m^2 and a history of gestational diabetes. Her mother and sister both have T2D. Two weeks ago, her A1C was 7.4%. Her fasting glucose concentration today is 178 mg/dL. She is asymptomatic. Which is the best course of action?

A. Diagnose T2D and begin treatment.

B. Diagnose T1D and begin treatment.

C. Obtain another A1C today.

D. Obtain another glucose concentration another day.

13. A 42-year-old man has a history of T2D. His current therapy includes metformin 1000 mg twice daily, glyburide 10 mg twice daily, and aspirin 81 mg once daily. Today, his A1C is 6.9%, blood pressure is 126/78 mm Hg, and fasting lipid panel is as follows: total cholesterol 212 mg/dL, low-density lipoprotein cholesterol (LDL) 98 mg/dL, high-density lipoprotein cholesterol (HDL) 45 mg/dL, and triglycerides (TG) 145 mg/dL. Which would be most appropriate for this patient?

A. Add insulin detemir 10 units once daily.

B. Add lisinopril 10 mg once daily.

C. Add atorvastatin 10 mg once daily.

D. Add fenofibrate 145 mg once daily.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-centered pharmacotherapy
    a. Task 1 with knowledge of:
        i. Anatomy, physiology, and pathophysiology
        ii. Disease processes, including drug-induced diseases
        iii. Pharmacology and toxicology
        iv. Evidence-based standards of care and clinical pathways
        v. Allergies and adverse drug reactions
        vi. Interpretation of laboratory tests, diagnostics, and procedures
        vii. Drug interactions
        viii. Nonpharmacologic treatments
        ix. Preventive care (e.g., screening, immunizations)
        x. Patient-specific goals of care and prioritization of needs
    b. Task 4 with knowledge of:
        i. Response to therapy and implications for therapeutic goals
        ii. Interpretation of laboratory tests, diagnostics, and procedures
        iii. Changes in patient clinical status
        iv. Disease progression or resolution
        v. Drug interactions
        vi. Adverse drug reactions
    c. Systems and patient-care problems:
        i. Thyroid disorders
        ii. Diabetes insipidus
        iii. Pituitary gland disorders
        iv. Adrenal gland disorders
        v. Obesity
        vi. Polycystic ovary syndrome
        vii. Diabetes (types 1 and 2)
        viii. Treatment of DM complications
2. Domain 3: System-based standards and population-based pharmacotherapy
    a. Task 1 with knowledge of laws and regulations

I. THYROID DISORDERS

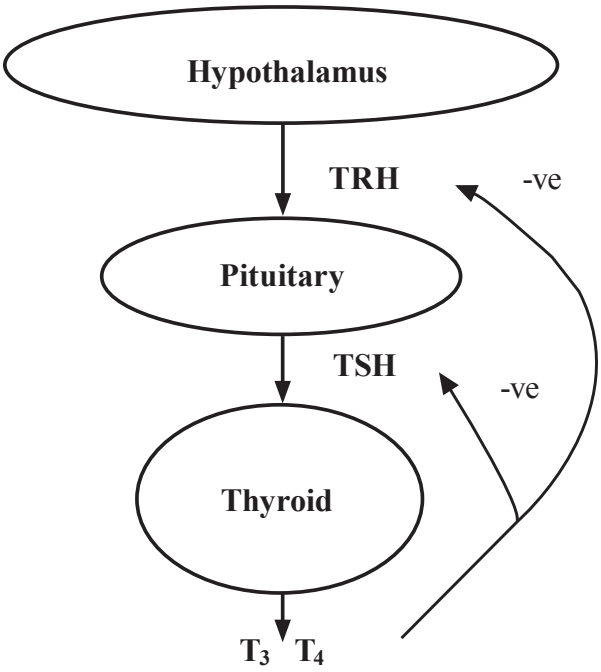

Figure 1. Hypothalamus-pituitary-thyroid axis.

[a]T_4 is converted to T_3 by peripheral tissue. Only unbound (free) thyroid hormone is biologically active.

T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; -ve = negative feedback loop.

Patient Case

1. A 43-year-old non-pregnant woman has received a diagnosis of Graves disease. She is reluctant to try ablative therapy and wants to try oral pharmacotherapy first. Her thyroid laboratory values today include TSH 0.22 mIU/L (normal 0.5–4.5 mIU/L) and free T_4 3.2 ng/dL (normal 0.8–1.9 ng/dL). She is anxious and always feels warm when others say it is too cold. Which is best for initial treatment of her condition?
   A. Lugol's solution.
   B. Propylthiouracil.
   C. Atenolol.
   D. Methimazole.

A. Hyperthyroid Disorders (thyrotoxicosis)
   1. Classification
      a. Toxic diffuse goiter (Graves disease): Most common hyperthyroid disorder
         i. Autoimmune disorder
         ii. Thyroid-stimulating antibodies directed at thyrotropin receptors mimic TSH and stimulate triiodothyronine (T_3) and T_4 production.
      b. Pituitary adenomas: Produce excessive TSH secretion that does not respond to normal T_3 negative feedback
      c. Toxic adenoma: Nodule in thyroid, autonomous of pituitary, and TSH
      d. Toxic multinodular goiter (Plummer disease): Several autonomous follicles that, if large enough, cause excessive thyroid hormone secretion

e. Painful subacute thyroiditis: Self-limiting inflammation of the thyroid gland caused by viral invasion of the parenchyma, resulting in the release of stored hormone
f. Drug induced (e.g., excessive exogenous thyroid hormone dosages, amiodarone therapy)

2. Diagnosis
   a. Elevated free T_4 serum concentrations
   b. Suppressed TSH concentrations (except in TSH-secreting adenomas)
   c. If examination and history do not provide the exact etiology, radioactive iodine uptake can be used.
      i. Radioactive iodine uptake elevated if thyroid gland is actively and excessively secreting T_4 and/or T_3: Graves disease, TSH-secreting adenoma, toxic adenoma, multinodular goiter
      ii. Radioactive iodine uptake is suppressed in disorders caused by thyroiditis or hormone ingestion.
   d. Can also assess for the presence of various thyroid-related antibodies (thyroid stimulating, thyrotropin receptor, or thyroperoxidase), thyroglobulin, and thyroid biopsy
3. Clinical presentation
   a. Weight loss or increased appetite
   b. Lid lag
   c. Heat intolerance
   d. Goiter
   e. Fine hair
   f. Heart palpitations or tachycardia
   g. Nervousness, anxiety, insomnia
   h. Menstrual disturbances (lighter or more infrequent menstruation, amenorrhea) caused by hypermetabolism of estrogen
   i. Sweating or warm, moist skin
   j. Exophthalmos, pretibial myxedema in Graves disease
4. Therapy goals
   a. Minimize or eliminate symptoms, improve quality of life
   b. Minimize long-term damage to organs (heart disease, arrhythmias, sudden cardiac death, bone demineralization, and fractures)
   c. Normalize free T_4 and TSH concentrations
5. Therapeutics
   a. Ablative therapy: Common treatment for Graves disease, toxic nodule, multinodular goiter; radioactive iodine ablative therapy and surgical resection for adenomas according to patient preferences or comorbidities. Ablative therapy often results in hypothyroidism.
   b. Thyroidectomy
   c. Antithyroid pharmacotherapy can be used for:
      i. Those awaiting ablative therapy or surgical resection
         (a) Depletes stored hormone
         (b) Minimizes risk of posttreatment hyperthyroidism caused by thyroiditis
      ii. Those who are not ablative or surgical candidates (e.g., serious cardiovascular disease, candidate unlikely to be adherent to radiation safety)
      iii. When ablative therapy or surgical resection fails to normalize thyroid function
      iv. Those with a high probability of remission with oral therapy for Graves disease
         (a) Mild disease
         (b) Small goiter
         (c) Low or negative antibody titers
         (d) Women
      v. Those with limited life expectancy
      vi. Those with moderate to severe active Graves ophthalmopathy

d. Thioureas (i.e., propylthiouracil, methimazole)
   i. Mechanism of action: Inhibits iodination and synthesis of thyroid hormones; propylthiouracil can block T_4/T_3 conversion in the periphery as well at high doses
   ii. Dosing
      (a) Propylthiouracil
         (1) Initial: 50–150 mg by mouth three times daily
         (2) Once euthyroid, can reduce to 50 mg two or three times daily
         (3) Recommended over methimazole in the first trimester of pregnancy because of the risk of embryopathy; can change to methimazole in second trimester
      (b) Methimazole
         (1) Preferred agent for Graves disease according to the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association for most patients
         (2) Initial: 10–30 mg by mouth once daily (use higher dose in those with higher baseline free T4 concentrations)
         (3) Once euthyroid, may reduce to 5–10 mg/day
      (c) Monthly dosage titrations as needed (depending on symptoms and free T_4 concentrations);
         (1) TSH may remain low for months after therapy begins
         (2) Early in therapy, total T3 may be a better marker of efficacy than free T4.
   iii. Adverse effects
      (a) Hepatotoxicity risk (boxed warning for PTU): Consider baseline liver function tests Routine evaluation of liver function while receiving antithyroid agents has not been shown to prevent severe hepatotoxicity.
      (b) Rash
      (c) Arthralgia, lupus-like symptoms
      (d) Fever
      (e) Agranulocytosis early in therapy (usually within 3 months): Guidelines recommend a baseline complete blood cell count; no routine monitoring recommended. Can repeat if patient becomes febrile or develops pharyngitis
      (f) Acute pancreatitis with methimazole
   iv. Efficacy
      (a) Slow onset in reducing symptoms (weeks). Maximal effect may take 4–6 months.
      (b) Neither drug appears superior to the other in efficacy.
      (c) On a milligram-to-milligram basis, methimazole is 10-fold more potent than propylthiouracil.
      (d) Remission rates low: 20%–30%. Remission is defined as normal TSH and T_4 for 1 year after discontinuing antithyroid therapy.
      (e) Therapy duration in Graves disease (oral agents unlikely to cause remission in those with nodular thyroid disease)
         (1) Usually 12–18 months; length of trial might not affect remission rate
         (2) Consider trial off oral therapy if TSH is normal; antibody titers can help guide decision.
         (3) Monitor thyroid concentrations every 1–3 months for up to 12 months for relapse (abnormal TSH or T_4 return).

e. Nonselective β-blockers (primarily propranolol; sometimes nadolol)
   i. Mechanism of action: Blocks many hyperthyroidism manifestations mediated by β-adrenergic receptors; also may block (less active) T_4 conversion to (more active) T_3 when used at high doses
   ii. Propranolol dosing
      (a) Initial: 20–40 mg by mouth three or four times daily
      (b) Maximal: 240–480 mg/day

iii. Adverse effects (see Hypertension section in Chronic Care in Cardiology chapter)
iv. Efficacy
(a) Used primarily for symptomatic relief (e.g., palpitations, tachycardia, tremor, anxiety)
(b) Guidelines recommend use in all symptomatic patients, especially older adults and others with heart rates greater than 90 beats/minute or existing cardiovascular disease. Also recommended for use before ablative iodine therapy in those who are extremely symptomatic or have a free T_4 2–3 times the upper limit of normal
(c) Poor remission rates: 20%–35%
(d) Primary role is treatment of thyroiditis, which is usually self-limiting, and for acute management of symptoms during thyroid storm (see the text that follows).
(e) Alternatives to β-blockers: Clonidine, non-dihydropyridine calcium channel blocker

f. Iodines and iodides (e.g., Lugol's solution, saturated solution of potassium iodide)
i. Mechanism of action: Inhibits the release of stored thyroid hormone. Minimal effect on hormone synthesis. Helps decrease vascularity and size of gland before surgery
ii. Dosing
(a) Lugol's solution (6.3–8 mg of iodide per drop)
(b) Saturated solution of potassium iodide (38–50 mg of iodide per drop)
(c) Potassium iodide tablets: 130-mg tablets contain 100 mg of iodide.
(d) Usual daily dose: 120–400 mg mixed with juice or water, split three times daily
iii. Adverse effects
(a) Hypersensitivity
(b) Metallic taste
(c) Soreness or burning in mouth or tongue
(d) Do not use in the days before ablative iodine therapy (may reduce uptake of radioactive iodine).
iv. Efficacy
(a) Limited efficacy after 7–14 days of therapy because thyroid hormone release will resume
(b) Primary use is temporary before surgery (7–10 days) to shrink the gland.
(c) Can be used after ablative therapy (3–7 days) to inhibit thyroiditis-mediated release of stored hormone
(d) Used acutely in thyroid storm

B. Subclinical Hyperthyroidism
1. Definition: Low (below lower limit of reference range) or undetectable TSH with normal T_4
2. Risk
a. Associated with elevated risk of atrial fibrillation in patients older than 60
b. Associated with elevated risk of bone fracture in postmenopausal women
c. Conflicting data about mortality risk
3. Treatment similar to treatment of overt hyperthyroidism
a. Oral antithyroid drug therapy alternative to ablative therapy in young patients with Graves disease
b. β-Blockers may help control cardiovascular morbidity, especially with atrial fibrillation.
4. If untreated, screen regularly for the development of overt hyperthyroidism (elevated free T_4 concentrations).

C. Thyroid Storm
1. Severe and life-threatening decompensated thyrotoxicosis. Mortality rate may be as high as 20%.
2. Precipitating causes: Trauma, infection, antithyroid agent withdrawal, severe thyroiditis, postablative therapy (especially if inadequate pretreatment)
3. Presentation: Fever, tachycardia, vomiting, dehydration, coma, tachypnea, delirium

4. Pharmacotherapy
    a. Propylthiouracil
        i. 500- to 1000-mg loading dose; then 250 mg every 4 hours
        ii. Blocks new hormone synthesis
        iii. Can use methimazole 60–80 mg daily
    b. Iodide therapy 1 hour after propylthiouracil initiation (dosed as stated earlier) to block hormone release
    c. β-Blocker therapy: Propranolol or esmolol commonly used to control symptoms and block conversion of T_4 to T_3
    d. Acetaminophen as antipyretic therapy, if needed (avoid nonsteroidal anti-inflammatory drugs because of displacement of protein-bound thyroid hormones)
    e. Corticosteroid therapy: Hydrocortisone 300-mg intravenous loading dose; then 100 mg every 8 hours (or equivalent dosages of, for example, dexamethasone, prednisolone). Provides prophylaxis against relative adrenal insufficiency and can block conversion of T_4 to T_3

Patient Case

2. A 63-year-old woman has Hashimoto disease. Her thyroid laboratory values today include TSH 10.6 mIU/L (normal 0.5–4.5 mIU/L) and free T_4 0.5 ng/dL (normal 0.8–1.9 ng/dL). She feels consistently rundown and has dry skin that does not respond to the use of hand creams. Which is the best drug for initial treatment of her condition?

    A. Levothyroxine.

    B. Liothyronine.

    C. Desiccated thyroid.

    D. Methimazole.

D. Hypothyroid Disorders
1. Classification
    a. Hashimoto disease: Most common hypothyroid disorder in areas with iodine sufficiency
        i. Autoimmune-induced thyroid injury resulting in decreased thyroid secretion
        ii. Disproportionately affects women
    b. Iatrogenic: Thyroid resection or radioiodine ablative therapy for hyperthyroidism
    c. Iodine deficiency most common cause worldwide
    d. Secondary causes
        i. Pituitary insufficiency (failure to produce adequate TSH secretion, called by some a central or secondary hypothyroidism)
        ii. Drug induced (e.g., amiodarone, lithium)
2. Diagnosis
    a. Low free T_4 serum concentrations
    b. Elevated TSH concentrations, typically seen as first laboratory abnormality, usually greater than 10 mIU/L (normal or low if central hypothyroidism is the cause)
    c. Thyroid antibodies such as antithyroid peroxidase and antithyroglobulin autoantibodies
    d. Screen patients older than 60, especially women (many different screening recommendations are given by various professional groups with little consensus).

3. Clinical presentation
    a. Cold intolerance
    b. Dry skin
    c. Fatigue, lethargy, weakness
    d. Weight gain
    e. Bradycardia
    f. Slow reflexes
    g. Coarse skin and hair
    h. Periorbital swelling
    i. Menstrual disturbances (more frequent or longer menstruation, painful menstruation, menorrhagia) caused by hypometabolism of estrogen
    j. Goiter (primary hypothyroidism)
4. Therapy goals
    a. Minimize or eliminate symptoms; improve quality of life
    b. Minimize long-term damage to organs (myxedema coma, heart disease)
    c. Normalize free T_4 and TSH concentrations
5. Therapeutics
    a. Levothyroxine (drug of choice)
        i. Mechanism of action: Synthetic T_4
        ii. Dosing
            (a) Initial
                (1) In otherwise healthy adults, 1.6 mcg/kg (use ideal body weight) per day
                (2) In patients age 50–60, consider 50 mcg/day.
                (3) In those with existing cardiovascular disease, consider 12.5–25 mcg/day.
            (b) For optimal bioavailability, usually dosed in the morning on an empty stomach 30–60 minutes before breakfast or at bedtime 3–4 hours after last meal; dosed separately from other medications (particularly calcium or iron supplements and antacids)
            (c) Dosage titration depending on response (control of symptoms, normalization of TSH and free T_4)
            (d) Can increase or decrease in 12.5- to 25-mcg/day increments, or consider increase or decrease in 10%–15% of weekly dose
            (e) Daily requirements are higher in pregnancy (separate guidelines available for treating thyroid disorders in pregnancy).
            (f) For hospitalized patients already receiving levothyroxine but for whom oral administration not an option, the intravenous dose is 75% of the oral dose.
        iii. Monitoring
            (a) 4–8 weeks is appropriate to assess patient response in TSH after initiating or changing therapy (about a 7-day half-life for T_4). May take longer for TSH to achieve steady-state concentrations
            (b) Use free T_4 rather than TSH if central or secondary hypothyroidism; obtain sample before daily dosing of levothyroxine
        iv. Adverse effects
            (a) Hyperthyroidism
            (b) Cardiac abnormalities (tachyarrhythmias, angina, myocardial infarction)
            (c) Linked to risk of fractures (usually at higher dosages or over-supplementation)
        v. Efficacy: If levothyroxine is properly dosed, most patients will maintain TSH and free T_4 in the normal ranges and experience symptomatic relief.
        vi. Considered drug of choice because of its adverse effect profile, cost, lack of antigenicity, and uniform potency

vii. Bioequivalence
(a) Guidelines recommend brand-name levothyroxine or consistent use of specific generic product.
(b) Although legal, guidelines recommend against changing from brand to generic and vice versa. It is recommended to stay with one product throughout therapy.
(c) TSH concentrations in bioequivalence testing were never obtained; small changes in T_4 between products can significantly change the TSH. Pharmacokinetic studies were conducted in healthy subjects with normal thyroid function.

b. Liothyronine (synthetic T_3), liotrix (synthetic T_4/T_3), and desiccated thyroid are not recommended by leading professional organizations or clinical guidelines. If converting from dessicated thyroid preparation to levothyroxine, 60 mg of dessicated thyroid is about equal to 100 mcg of levothyroxine.

E. Subclinical Hypothyroidism
1. Definition: Elevated TSH (above upper limit of reference range) with normal T_4. Often the result of early Hashimoto disease
2. Risk
a. TSH greater than 7.0 mIU/L in older adults associated with elevated risk of heart failure
b. TSH greater than 10 mIU/L associated with elevated risk of coronary heart disease
3. Treatment of subclinical hypothyroidism is controversial because benefits in identified patients are inconclusive. An association between the use of levothyroxine and a reduction in heart disease in younger patients (40–70 years of age) does appear to exist, but not in older patients (older than 70).
4. Whom to treat
a. TSH 10 mIU/L or greater
b. TSH 4.5–10 mIU/L and
i. Symptoms of hypothyroidism
ii. Antithyroid peroxidase antibodies present
iii. History of cardiovascular disease, heart failure, or risk factors for such
c. Initial daily doses of 25–75 mcg of levothyroxine recommended
5. If untreated, screen regularly for the development of overt hypothyroidism (decreased free T_4 concentrations).

F. Myxedema Coma
1. Severe and life-threatening decompensated hypothyroidism; mortality rate 30%–60%
2. Precipitating causes: Trauma, infections, heart failure, medications (e.g., sedatives, narcotics, anesthesia, lithium, amiodarone)
3. Presentation: Coma is not required and is uncommon, despite terminology; altered mental state (very common); diastolic hypertension; hypothermia; hypoventilation
4. Pharmacotherapy
a. Intravenous thyroid hormone replacement
i. T_4: 200- to 400-mcg intravenous loading dose, followed by 1.6 mcg/kg daily. Lower the initial dose in frail patients or patients with established cardiovascular disease. Intravenous doses are around 75% of oral administration.
ii. Some advocate the use of T_3 over T_4, given that T_3 is more biologically active and that T_4/T_3 conversion may be suppressed in myxedema coma. Cost and availability limit intravenous T_3 use.
b. Antibiotic therapy: Given common infectious causes, some clinicians advocate empiric therapy with broad-spectrum antibiotics.

c. Corticosteroid therapy
   i. Hydrocortisone 100 mg every 8 hours (or equivalent steroid) or doses appropriate for the stressed state
   ii. Can be discontinued if random cortisol concentration not depressed
d. Adjust levothyroxine dose on the basis of serum T_3 measured every 1 or 2 days.

II. PITUITARY GLAND DISORDERS

Table 1. Basic Pituitary Gland (Anterior) Hormone Physiology

Anterior Pituitary Hormone	Primary Function(s)	Hypothalamic Stimulator	Primary Secretion Inhibitor
Growth hormone (GH)	Promote tissue growth	GH-releasing hormone	Somatostatin Insulin-like growth factor-1
Adrenocorticotropic hormone (ACTH)	Stimulate adrenal cortisol and androgen release	Corticotropin-releasing hormone	Cortisol
Thyroid-stimulating hormone (TSH)	Metabolic stability	Thyrotropin-releasing hormone	Triiodothyronine
Prolactin	Regulate lactation	Thyrotropin-releasing hormone	Dopamine
Follicle-stimulating hormone	Maturation of ovarian follicles Sperm production	Gonadotropin-releasing hormone	Inhibin Estrogens
Luteinizing hormone	Secretion of sex steroids	Gonadotropin-releasing hormone	Estrogens and progestins Testosterone

A. Classification (focus on the common anterior pituitary disorders)
   1. Hypersecretory diseases
      a. Acromegaly and gigantism: Usually caused by growth hormone (GH)-secreting pituitary adenoma
      b. Hyperprolactinemia
         i. Most common cause is prolactinomas (prolactin-secreting pituitary tumor).
         ii. Drug induced (e.g., serotonin reuptake inhibitors and some antipsychotics)
         iii. Central nervous system lesions
   2. Hyposecretory disease
      a. GH deficiency
         i. Congenital abnormality caused by GH gene deletion, GH-releasing hormone deficiency
         ii. Other causes are pituitary aplasia, head trauma, and central nervous system infection.
         iii. Idiopathic
      b. Panhypopituitarism: Result of partial or complete loss of anterior and posterior pituitary function. Can be caused by primary pituitary tumor, ischemic necrosis of the pituitary, trauma from surgery, or irradiation. Results in adrenocorticotropic hormone (ACTH) deficiency, GH deficiency, hypothyroidism, gonadotropin deficiency

B. Acromegaly
   1. Diagnosis and clinical presentation
      a. Failure of an oral glucose tolerance test (OGTT) to suppress GH serum concentrations but with elevated insulin-like growth factor-1 (IGF-1) (GH serum concentrations alone are unreliable, given the pulsatile pattern of release in the body.)

b. Clinical presentation (Note that the disease has a slow onset, and many symptoms do not appear for years.)
    i. Excessive sweating
    ii. Osteoarthritis, joint pain, paresthesias, or neuropathies
    iii. Coarsening of facial features
    iv. Increased hand volume or ring size, increased shoe size
    v. Hypertension, heart disease, cardiomyopathy
    vi. Sleep apnea
    vii. T2D

2. Therapy goals
    a. Reduce GH and IGF-1 concentrations
    b. Decrease mortality
    c. Improve clinical symptoms
    d. Normalize IGF-1 concentrations and suppressed GH concentrations after OGTT
3. Therapeutics
    a. Treatment of choice is surgical resection of tumor, if causative.
    b. Pharmacotherapy usually reserved for:
        i. Control before surgery or irradiation
        ii. When surgery is not possible (usually requires lifelong pharmacotherapy)
        iii. Surgical failures or relapses after period of remission after surgery
    c. Dopamine agonists (e.g., bromocriptine, cabergoline)
        i. Mechanism of action: Dopamine agonist that, in acromegaly, causes paradoxical decrease in GH production
        ii. Dosing (bromocriptine is most commonly used agent)
            (a) Initial: 1.25 mg/day by mouth
            (b) Maximal: 20–30 mg/day (can titrate once or twice weekly, as needed)
        iii. Adverse effects
            (a) Fatigue, dizziness, nervousness
            (b) Diarrhea, abdominal pain
        iv. Efficacy: Normalization of IGF-1 concentrations in about 10% of patients. More than 50% of patients experience symptomatic relief.
    d. Somatostatin analog (e.g., octreotide)
        i. Mechanism of action: Blocks GH secretion; 40 times more potent than endogenous somatostatin
        ii. Dosing
            (a) Initial: 50–100 mcg subcutaneously every 8 hours or 20 mg orally twice daily
            (b) Maximal: Little benefit greater than 600 mcg/day or 80 mg daily with oral administration
            (c) If response is adequate, can be changed to long-acting octreotide formulation administered once monthly
            (d) Orally with a glass of water on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal
        iii. Adverse effects
            (a) Diarrhea, nausea, cramps, flatulence, fat malabsorption
            (b) Arrhythmias
            (c) Hypothyroidism
            (d) Biliary tract disorders
            (e) Changes in serum glucose concentrations (usually reduces)
        iv. Efficacy: 50%–60% of patients experience normalization of IGF-1 concentrations with good symptomatic relief as well. May shrink tumor mass in some patients

e. GH receptor antagonist (e.g., pegvisomant)
   i. Mechanism of action: GH derivative binds to liver GH receptors and inhibits IGF-1
   ii. Dosing
      (a) Initial: 40 mg once-daily subcutaneous injection loading dose and then 10 mg once daily
      (b) Maximal: 30 mg/day
   iii. Adverse effects
      (a) Nausea, vomiting
      (b) Flulike symptoms
      (c) Reversible elevations in hepatic transaminase
   iv. Efficacy: More than 95% of patients attain normal IGF-1 concentrations, and most have improved symptoms.

Patient Case

3. A 28-year-old woman presents with acne, facial hair growth, and irregular menses that have lasted for 6–7 months. Her medical history includes hypertension and depression. Her pituitary and thyroid tests results have been negative. Her current medications include amlodipine and fluoxetine. Her prolactin concentration today is 112 ng/mL (normal 15–25 ng/mL). Which is the most likely cause of her elevated prolactin concentration?

   A. Amlodipine.

   B. Prolactin-secreting adenoma.

   C. Pregnancy.

   D. Fluoxetine.

C. Hyperprolactinemia
   1. Causes
      a. Direct: Pituitary tumor (lactotroph adenoma = prolactinoma accounting for around 40% of tumors)
      b. Indirect: Drug induced (most common nontumor cause), renal failure, hypothyroidism, breastfeeding
      c. Potential causative drugs: Typical antipsychotics, opiates, non-dihydropyridine calcium channel blockers, antidepressants
   2. Diagnosis and clinical presentation
      a. Elevated serum prolactin concentrations; may be challenging to find specific cause (unless drug induced)
      b. Clinical presentation
         i. Amenorrhea, anovulation, infertility, hirsutism, and acne in women
         ii. Erectile dysfunction, decreased libido, gynecomastia, and reduced muscle mass in men
         iii. Headache, visual disturbances, bone loss
   3. Therapy goals
      a. Normalize prolactin concentrations
      b. Normalize gonadotropin secretion
      c. Relieve symptoms
      d. Decrease tumor size
   4. Therapeutics
      a. Surgical resection of tumor, if tumor is very large, causes severe compression of adjacent tissues, or patient does not respond to pharmacotherapy
      b. Discontinue causative agent if drug induced.
         i. Recheck prolactin concentration 3 days after discontinuation.
         ii. Select agent with similar action but no known effect on prolactin concentrations.
         iii. If discontinuation of causative agent not feasible, consider dopamine agonist

c. Dopamine agonists (preferred to surgery in most cases)
    i. Cabergoline (preferred agent according to the Endocrine Society guidelines, long-acting oral agent; adverse effect profile similar to that for bromocriptine but fewer gastrointestinal [GI] adverse effects)
        (a) Initial: 0.5 mg once weekly
        (b) Maximal: 4.5 mg/week
    ii. Bromocriptine (see previous text)
    iii. Efficacy: May restore fertility in more than 90% of women. Long-term cure rates are around 60% for smaller tumors, around 25% for larger tumors. Cabergoline may be easier for patients to take, given its weekly administration.
    iv. Consider tapering or discontinuing after 2 years of therapy if asymptomatic, prolactin concentrations normalized, and no tumor remnant by imagery

D. GH Deficiency:
1. Diagnosis and clinical presentation
    a. Decreased GH concentrations after provocative pharmacologic challenge (e.g., insulin, clonidine, GH-releasing hormone)
    b. Clinical presentation
        i. Delayed growth velocity or short stature
        ii. Central obesity
        iii. Immaturity of the face or prominence of the forehead
2. Therapy goals
    a. Increase growth velocity
    b. Increase final adult height when treating children
3. Therapeutics: Recombinant GH (somatropin)
    a. Dosing
        i. Depends on which of the various products are selected (dosed subcutaneously or intramuscularly once daily)
        ii. When to discontinue therapy on the basis of growth velocity is controversial.
        iii. Once- or twice-monthly long-acting depot formulation is also available.
    b. Adverse effects
        i. Arthralgia, injection-site pain
        ii. Rare but serious cases of idiopathic intracranial hypertension have been reported.
    c. Efficacy: All products are considered equally efficacious.

III. ADRENAL GLAND DISORDERS

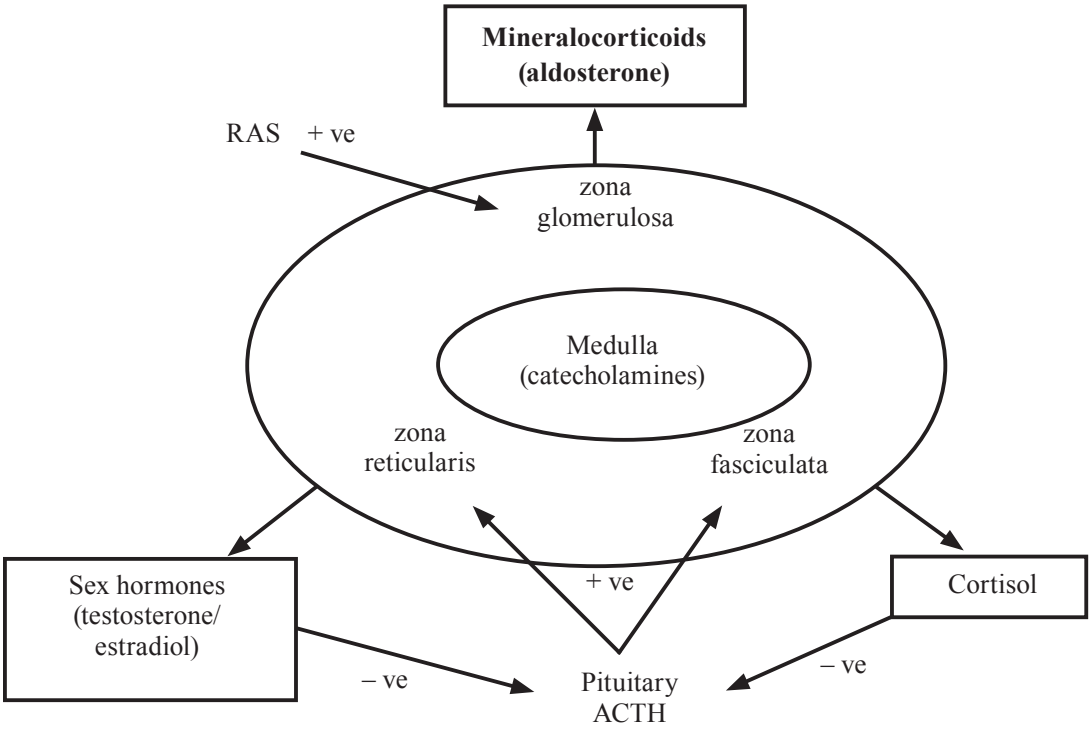

Figure 2. Basic adrenal cortex hormone physiology.
ACTH = adrenocorticotropic hormone; RAS = renin-angiotensin system; +ve = positive stimulation; –ve = negative feedback.

Patient Case

4. A 44-year-old man has consistently high blood pressure (172/98 mm Hg today), despite his documented adherence to two maximal-dose blood pressure medications. He has frequent headaches, increased thirst, and fatigue. His urine free cortisol is 45 mcg/24 hours (normal range 20–90) and plasma aldosterone/renin ratio is 125 (normal is less than 25). Which most likely caused this patient's uncontrolled hypertension?

   A. Cushing syndrome.

   B. Addison disease.

   C. Hyperprolactinemia.

   D. Hyperaldosteronism.

A. Hypersecretory Cortisol Diseases (Cushing syndrome)

1. Classification
   a. ACTH-dependent: Result of excessive ACTH secretion
      i. Pituitary corticotroph adenoma (Cushing disease)
      ii. Ectopic ACTH syndrome (extrapituitary tumor)
   b. ACTH-independent: Result of excessive cortisol secretion or exogenous steroids
      i. Unilateral adrenocortical tumors
      ii. Bilateral adrenal hyperplasia or dysplasia
      iii. Exogenous steroid administration

2. Diagnosis and clinical presentation
    a. Presence of hypercortisolism through 24-hour urinary free cortisol concentration
    b. Differentiate etiology (key to treatment options).
        i. Complex and beyond the scope of this chapter
        ii. Plasma ACTH concentrations (normal or elevated in ACTH-dependent)
        iii. Pituitary magnetic resonance imaging (Cushing syndrome vs. ectopic ACTH syndrome)
        iv. Overnight dexamethasone suppression test
        v. Late-night salivary cortisol concentration
        vi. 24-hour urinary free cortisol (low sensitivity)
    c. Clinical presentation
        i. Central obesity and facial rounding quite common
        ii. Peripheral obesity and fat accumulation
        iii. Myopathies
        iv. Osteoporosis, back pain, compression fracture
        v. Abnormal glucose tolerance or diabetes
        vi. Amenorrhea and hirsutism in women
        vii. Lower abdominal pigmented striae (red to purple)
        viii. Hypertension (principal cause of morbidity and mortality)
3. Therapy goals
    a. Reduce morbidity and mortality and eliminate cause
    b. Reverse clinical features
    c. Normalize biochemical changes (when possible)
    d. Achieve long-term control without recurrence (remission when possible)
4. Therapeutics
    a. If excessive exogenous corticosteroid use is causative, discontinue or minimize use.
    b. Surgical resection of causative area or tumor is usual treatment of choice.
    c. Pharmacotherapy is usually reserved on the basis of the same criteria listed earlier for pituitary adenomas.
    d. Inhibit ACTH secretion
        i. Pasireotide
            (a) Mechanism of action: Somatostatin analog blocks ACTH secretion from pituitary, leading to decreased circulating cortisol concentrations (better selectivity to pertinent somatostatin receptors than other analogs such as octreotide). Pasireotide is usually not effective for adrenally caused Cushing syndrome. Pasireotide's main role is in Cushing disease, but its role according to the guidelines is yet to be determined.
            (b) Dosing: 0.6–0.9 mg twice-daily subcutaneous injection (dose adjustments based on urinary free cortisol and symptom improvements)
            (c) Adverse effects: Hyperglycemia, hypocorticalism, diarrhea, nausea, gallstones, headache, bradycardia
            (d) Obtain an electrocardiogram, FPG, A1C, liver function tests, and gallbladder ultrasonography before initiating therapy.
            (e) Self-monitor BG values every week for first 2–3 months, and then periodically obtain liver function tests 1–2 weeks after starting therapy; then obtain them monthly for 2–3 months and then every 6 months. Repeat gallbladder ultrasonography at 6- to 12-month intervals.
        ii. Cabergoline (see dosing and ADR profile listed earlier)
    e. Inhibit cortisol synthesis
        i. Osilodrostat
            (a) Mechanism of action: Hinders cortisol production by blocking the 11-β-hydroxylase enzyme

(b) Dosing
(1) Initial: 2 mg twice daily by mouth
(2) Maximal: 30 mg twice daily
(c) Adverse effects
(1) Headache
(2) Nausea/vomiting
(3) Fatigue
(4) QT prolongation (obtain baseline electrocardiogram 1 week after initiating therapy)

ii. Ketoconazole
(a) Mechanism of action: In addition to its antifungal activity, it hinders cortisol production by inhibiting 11- and 17-hydroxylase.
(b) Dosing
(1) Initial: 200 mg twice daily by mouth
(2) Maximal: 400 mg three times daily
(c) Adverse effects
(1) Gynecomastia
(2) Abdominal discomfort
(3) Reversible hepatic transaminase elevations
(4) Be aware of potential drug-drug interactions.

iii. Mitotane
(a) Mechanism of action: Inhibits 11-hydroxylase but also has some direct adrenolytic activity
(b) Dosing
(1) Initial: 500–1000 mg/day by mouth (some use much higher daily dosages, but they are not well tolerated)
(2) Maximal: 9–12 g/day
(c) Adverse effects
(1) Adrenocortical atrophy: Can persist on discontinuation and, in severe cases, may necessitate androgen and glucocorticoid replacement
(2) Anorexia
(3) Ataxia
(4) Abdominal discomfort
(5) Lethargy

iv. Etomidate
(a) Mechanism of action: Similar to ketoconazole, inhibits 11-hydroxylase
(b) Dosing
(1) Initial: 0.03 mg/kg intravenously, followed by a 0.1-mg/kg/hour infusion
(2) Maximal: 0.3 mg/kg/hour
(c) Adverse effects
(1) Pain at injection site
(2) Nausea and vomiting
(3) Myoclonus
(4) Psychoses
(d) Given route of administration is usually reserved for when rapid control of cortisol concentrations is needed and oral therapy is problematic.

v. Metyrapone (by compassionate use only)
(a) Mechanism of action: Hinders secretion of cortisol by blocking final step in cortisol synthesis by inhibiting 11-hydroxylase activity

(b) Dosing
(1) Initial: 500 mg three times daily by mouth
(2) Average dose in Cushing syndrome is 2000 mg/day, but dose is about 4000 mg in ectopic ACTH syndrome.
(c) Adverse effects
(1) Hypoadrenalism
(2) Hypertension
(3) Worsening of hirsutism and acne if present before treatment
(4) Headache
(5) Abdominal discomfort

f. Efficacy is measured by control of symptoms and normalization of 24-hour urine-free cortisol concentrations.
g. Glucocorticoid replacement may be necessary if circulating cortisol is reduced to lower than physiologic concentrations.
h. Mifepristone for hyperglycemia associated with endogenous Cushing syndrome; proposed to limit binding of cortisol; can reduce insulin requirements and improve clinical symptoms associated with hyperglycemia

B. Hyperaldosteronism: Primary Aldosteronism
1. Classification
a. Bilateral adrenal hyperplasia (70% of cases)
b. Aldosterone-producing adenoma (30% of cases)
2. Diagnosis and clinical presentation
a. Elevated plasma aldosterone/renin ratio
b. Other features: Hypernatremia, hypokalemia, hypomagnesemia, glucose intolerance
c. Clinical presentation (can be asymptomatic)
i. Hypertension
ii. Muscle weakness or fatigue
iii. Headache
iv. Polydipsia
v. Nocturnal polyuria
3. Therapy goals (same as earlier for Cushing syndrome)
4. Therapeutics
a. Spironolactone (drug of choice)
i. Mechanism of action: Competitively inhibits aldosterone biosynthesis
ii. Dosing
(a) Initial: 25–50 mg/day by mouth
(b) Maximal: 400 mg/day
iii. Adverse effects
(a) Hyperkalemia
(b) Gynecomastia
(c) Abdominal discomfort
b. Eplerenone and amiloride are alternatives to spironolactone.

C. Hyposecretory Adrenal Disorders
1. Classification
a. Primary adrenal insufficiency (i.e., Addison disease)
i. Caused by autoimmune disorder, infection, or infarction
ii. Results in cortisol, aldosterone, and androgen deficiencies

   b. Secondary adrenal insufficiency
      i. Exogenous steroid use (from chronic suppression); oral, inhaled, intranasal, and topical administration
      ii. Surgery, trauma, infection, infarction
      iii. Results in impaired androgen and cortisol production
2. Diagnosis and clinical presentation (focus on Addison disease)
   a. Abnormal rapid cosyntropin (synthetic ACTH) stimulation test (blunted increase in cortisol concentrations) suggests adrenal insufficiency
   b. Clinical presentation
      i. Hyperpigmentation (caused by elevated ACTH concentrations)
      ii. Weight loss
      iii. Dehydration
      iv. Hyponatremia, hyperkalemia, elevated blood urea nitrogen
3. Therapy goals (same as earlier for Cushing syndrome)
4. Therapeutics (Table 2)
   a. Steroid replacement (replace cortisol loss)
      i. Oral administration is commonly dosed to mimic normal cortisol production circadian rhythm.
      ii. Two-thirds administered in the morning and one-third in the evening
         (a) This may cause periods of transient adrenal insufficiency or variable serum concentrations in some patients.
         (b) Daily cortisol production in average patient: 5–10 mg/m^2
   b. Hydrocortisone: 15 mg/day (use may reduce need for fludrocortisone compared with use of cortisone or prednisone)
      i. Cortisone acetate: 20 mg/day
      ii. Prednisone: 2.5 mg/day
      iii. Dexamethasone: 0.25–0.75 mg/day
   c. Fludrocortisone (replaces loss of mineralocorticoid): 0.05–0.2 mg/day by mouth
   d. For women with decreased libido or low energy levels because of androgen deficiency, dehydroepiandrosterone: 25–50 mg/day
   e. Efficacy can be measured by symptom improvement.
   f. Note that during times of stress or illness, corticosteroid dosages must be increased. Dose and route of administration depend on level of stress to the body.

Table 2. Comparative Glucocorticoid Dosing

Glucocorticosteroid	Relative Equivalent Dosing (mg)
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75

IV. OBESITY

A. Recent Guidelines
   1. American College of Cardiology/American Heart Association (ACC/AHA) and The Obesity Society 2013 guidelines; first significant guideline since 1998. Most of the therapeutic agents that follow were approved for obesity after the guideline was initiated and are not included.
   2. Endocrine Society 2015 guidelines are focused on new obesity agents. No specific recommendations of a particular agent over another, but a good review of the therapeutic options
   3. AACE/American College of Endocrinology 2016 guidelines. A comprehensive review of nonpharmacologic and pharmacologic therapy for obesity. Like the Endocrine Society guidelines, there are no specific recommendations regarding one agent over another.

B. Classification
   1. Based on BMI
   2. Normal: BMI 18.5–24.9 kg/m^2
   3. Overweight: BMI 25.0–29.9 kg/m^2
   4. Obesity
      a. Class I: BMI 30.0–34.9 kg/m^2
      b. Class II: BMI 35.0–39.9 kg/m^2
      c. Class III: BMI 40 kg/m^2 or greater

C. Therapy Goals
   1. Weight loss: Initial goal: 5%–10% decrease from baseline weight over 6 months
   2. Maintain lower weight in the long term
   3. Limit weight-induced comorbidities (e.g., T2D, hypertension, cardiovascular disease)

D. Nonpharmacologic Therapy (aimed at providing an energy deficit)
   1. Increased physical activity: 200–300 minutes per week (minimum 150)
   2. Dietary options: Any diet that has proven weight reduction data available is appropriate. No specific recommendations of one diet over another. Individualize according to patient preferences.
      a. Strive for at least a 500-kcal/day deficit.
      b. 1200–1500 kcal/day for women
      c. 1500–1800 kcal/day for men
   3. Behavioral intervention: According to ACC/AHA/The Obesity Society guidelines: Preferably in-person, high-intensity (at least 14 sessions in 6 months) comprehensive weight-loss intervention through group or individual sessions with a professional (e.g., dietitian, exercise specialist, health counselor)
   4. Surgery: Usually reserved for patients with severe obesity (BMI greater than 40 kg/m^2) or BMI of at least 35 kg/m^2 with at least one obesity-related comorbidity such as diabetes, hypertension, or obstructive sleep apnea
      a. Roux-en-Y gastric bypass (decreasing in frequency)
      b. Sleeve gastrectomy (now the most common surgery)
      c. Adjustable gastric banding

Patient Case

5. A patient takes the maximal daily dose of phentermine/topiramate for the treatment of obesity. The patient's baseline BMI is 36 kg/m^2 and weight is 115.7 kg (255 lb). Which best represents the minimum weight loss required to consider continuing treatment with this agent after 3 months of therapy?

   A. 3.2 kg (7 lb).

   B. 5.9 kg (13 lb).

   C. 7.7 kg (17 lb).

   D. 11.8 kg (26 lb).

E. Pharmacotherapy
   1. Always in conjunction with diet, physical activity, and behavioral therapy
   2. Medications should be reserved for those not achieving or sustaining weight reduction with adequate lifestyle modifications, in those with obesity, or in those with a BMI of at least 27 kg/m^2 with significant weight-related comorbidities (e.g., diabetes, hypertension, dyslipidemia).
   3. Medication selected according to risk-benefit profile should be approved by the U.S. Food and Drug Administration (FDA). After 1 year, approved agents should provide at least a statistically significant 5% weight loss difference from placebo, or at least 35% of treated subjects should achieve at least a 5% weight loss from baseline and twice that of placebo-treated subjects.
   4. Orlistat
      a. Mechanism of action: Reduced absorption of fat by inhibition of gastric and pancreatic lipases
      b. Dosing
         i. Prescription: 120 mg three times daily during or up to 1 hour after meals
         ii. Over the counter: 60 mg three times daily during or up to 1 hour after meals
      c. Adverse effects
         i. GI tract: Flatulence, oily stools, loose stools, fecal urgency, or incontinence (highly dependent on fat content of meal)
         ii. Reduced absorption of fat-soluble vitamins (A, D, E, and K): Use vitamin supplement before or well after use.
         iii. Hepatotoxicity, kidney stones (FDA warnings)
      d. Efficacy: 35%–54% of patients taking a prescription-strength product attained at least a 5% weight loss after 1 year of therapy, and 16%–25% attained at least a 10% weight loss.
   5. Phentermine/extended-release topiramate (schedule IV)
      a. Mechanism of action: Phentermine promotes appetite suppression and decreases food intake secondary to its sympathomimetic activity. Mechanism of topiramate is unknown, but it can cause appetite suppression and satiety through increased γ-aminobutyrate activity.
      b. Dosing (phentermine/topiramate): Should be taken in the morning to avoid insomnia
         i. Initial: 3.75/23 mg daily for 2 weeks; then increase to 7.5/46 mg daily
         ii. If at least a 3% weight loss not achieved after 12 weeks, can discontinue or increase to 11.25/69 mg daily for 2 weeks; then increase to 15/92 mg daily, if tolerated
         iii. If at least a 5% weight loss not achieved with 15/92 mg daily, discontinue use. Taper when discontinuing to avoid seizures.
         iv. Dosing in moderate hepatic or renal impairment: Do not exceed 7.5/46 mg daily.
      c. Adverse effects: Dry mouth, paresthesia, constipation, dysgeusia, insomnia, attention and memory disturbances, increased heart rate
      d. In women of childbearing age, obtain a negative pregnancy test before initiating and monthly thereafter because of fetal toxicity. Stress the importance of adequate contraception during use.

e. Efficacy: 9%–10% weight loss from baseline; 60%–70% attained at least a 5% weight loss after 1 year of treatment, and 37%–48% attained at least a 10% weight loss
f. Discontinue use if patient does not achieve at least a 5% weight loss after 12 weeks of use.

6. Bupropion/naltrexone
   a. Mechanism of action: Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)
   b. Dosing (8 mg naltrexone/90 mg bupropion tablets extended release)
      i. Dosage escalation at weekly intervals by 1 tablet daily
      ii. Initially, 1 tablet once daily
      iii. Target dosage: 2 tablets twice daily
   c. Adverse effects: Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth
   d. Precautions and contraindications: Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal. Avoid with chronic use of opioids.
   e. Efficacy: 5%–6% weight loss from baseline; 40%–55% attained at least a 5% weight loss after 56 weeks of therapy, 20%–25% attained at least a 10% weight loss
   f. Discontinue use if at least a 5% weight loss is not achieved after 12 weeks of use.
7. Liraglutide
   a. Mechanism of action: Glucagon-like peptide-1 (GLP-1) agonist (part of incretin system). Thought to cause satiety and delay gastric emptying. Used in treatment of T2D (see text that follows)
   b. Dosing (administered subcutaneously by pen device)
      i. Target dosage higher in obesity than in treatment of diabetes. Brand-name product for obesity is not approved for diabetes and vice versa.
      ii. Initially, 0.6 mg once daily; increase by 0.6 mg at weekly intervals
      iii. Target dosage for obesity: 3 mg daily
   c. Adverse effects: Nausea, vomiting, diarrhea, constipation, dyspepsia
   d. Precautions and contraindications
      i. See the Diabetes Mellitus section.
      ii. Obesity formulation should be avoided in patients receiving insulin (increased risk of hypoglycemia).
      iii. Do not use with other GLP-1 agonists used in the treatment of diabetes mellitus (DM).
   e. Efficacy
      i. Patients without diabetes: 8%–9% weight loss from baseline; 60%–65% attained at least a 5% weight loss after 56 weeks of treatment, and about 33% attained at least a 10% weight loss
      ii. Patients with diabetes: 6% weight loss from baseline; 54% attained at least a 5% weight loss after 56 weeks of treatment, and 25% attained at least a 10% weight loss. Only minimally more effective at A1C reduction than standard diabetes dosage (see text that follows for diabetes dosing)
   f. Discontinue use if the patient does not achieve at least a 4% weight loss after 16 weeks of therapy or if the patient cannot tolerate the target 3-mg daily dosage.
8. Diethylpropion (schedule IV), phentermine (schedule IV), phendimetrazine (schedule III)
   a. Should be used only for a limited time, up to 3 months, and avoid in those with abuse potential
   b. Clinical guidelines do not recommend their use.
   c. Adverse effects: Increased blood pressure, constipation, increased heart rate, dysrhythmias, abuse potential (avoid in patients with hypertension or a history of cardiovascular disease)
9. Other issues
   a. Concurrent use of obesity medications has not been studied.
   b. Comparative studies between agents are lacking (although liraglutide has been shown to reduce weight better than orlistat).
   c. Long-term safety of all agents is unknown.
   d. Consider obesity a chronic condition. Weight gain after discontinuation of agent is likely

10. Off-label medications used but not well studied specifically for obesity: Selective serotonin reuptake inhibitors, zonisamide, metformin, pramlintide
11. Lorcaserin was removed from the market in early 2020 after increased risk of some cancers was detected.

V. POLYCYSTIC OVARY SYNDROME

A. Background and Classification
   1. Can be a cause of infertility in up to 20% of infertile couples
   2. Mainly considered to be caused by androgen excess or hyperandrogenism
   3. Underlying cause appears to be insulin resistance (in patients with and without obesity), with subsequent compensatory insulin hypersecretion or increased insulin action. This increased action stimulates androgen secretion by the ovaries or adrenal cells, leading to increased luteinizing hormone (LH) secretion but normal or low follicle-stimulating hormone (FSH) concentrations, with a subsequent decrease in follicular maturation and anovulation.
   4. Has several potential comorbidities with endocrine and cardiovascular implications (e.g., T2D, obesity)
   5. Can affect 6%–10% of women (or more depending on diagnostic criteria used), making it one of the most prevalent endocrine disorders in young women
   6. Women younger than 50 are at higher cardiovascular disease risk.

B. Diagnosis
   1. Still somewhat under debate; no clear consensus
   2. 1990 National Institutes of Health criteria
      a. Hyperandrogenism or hyperandrogenemia
      b. Oligo-ovulation (infrequent or irregular ovulation)
      c. Exclusion of other secondary causes, particularly adrenal hyperplasia, Cushing syndrome, hyperprolactinemia
   3. 2003 Rotterdam criteria: Presence of at least two of the following and ruling out secondary causes
      a. Menstrual irregularity (oligo-ovulation or anovulation)
      b. Hyperandrogenism (clinical or biochemical signs)
      c. Polycystic ovaries (by transvaginal ultrasonography)
      d. Recommended by the Endocrine Society guideline
   4. 2006 Androgen Excess Society: Follow 1990 National Institutes of Health criteria, but recognize concerns brought about from the Rotterdam criteria.

C. Clinical Presentation
   1. Clinical signs of hyperandrogenism: Hirsutism, acne, pattern alopecia (can vary by ethnicity)
   2. Biochemical signs of hyperandrogenism (should not be used as the sole criterion because 20%–40% of patients with PCOS may be in the normal range)
      a. Elevated free or total serum testosterone
      b. LH/FSH ratio greater than 2
   3. Infrequent, irregular (e.g., late), or no ovulation, leading to irregular menses
   4. Infertility despite unprotected and frequent intercourse during the past year
   5. In patients with obesity (50%–80% of cases), prediabetes (impaired glucose tolerance) or T2D may be present.

D. Therapy Goals
   1. Normalize ovulation and menses
   2. Improve fertility in those who want to become pregnant
   3. Limit clinical signs
   4. Reduce progression to T2D (perhaps cardiovascular disease)

E. Nonpharmacologic Therapy
   1. Weight loss (5%–10%) important in patients who are overweight or have obesity
   2. Mechanical hair removal for hirsutism

F. Pharmacotherapy
   1. Fertility improvement
      a. Clomiphene citrate
         i. Mechanism of action: Induces ovulation as a selective estrogen receptor modulator that improves LH-FSH secretion
         ii. Dosing
            (a) 50 mg/day for 5 days starting on the third or fifth day of the menstrual cycle
            (b) Increase to 100 mg if ovulation does not occur after first cycle of treatment.
            (c) Maximal daily dosage: 150–200 mg/day
         iii. Adverse effects: Flushing, GI discomfort, vision disturbances, vaginal dryness, multiple pregnancies
         iv. Improved ovulation and pregnancy rates when used in combination with metformin
         v. Considered first-line treatment by the Endocrine Society 2013 recommendations
      b. Gonadotropin (e.g., recombinant FSH) or recombinant gonadotropin-releasing hormone therapy with or without clomiphene
         i. Mechanism of action: Normalizes LH/FSH ratio to stimulate ovulation
         ii. Dosing: Many dosing strategies used
         iii. Adverse effects: Multiple pregnancies, ovarian hypertrophy, miscarriage, mood swings, breast discomfort
      c. Letrozole
         i. Mechanism of action: Aromatase inhibitor prevents conversion of androgens to estrogen, which results in an increased secretion of FSH from the anterior pituitary; conflicting meta-analysis data on its effectiveness compared with clomiphene on pregnancy rates
         ii. Dosing: 2.5–5 mg daily
         iii. Adverse effects: Edema, sweating, constipation, nausea, arthralgias, headache
         iv. Considered the treatment of choice for ovulation induction by the American College of Obstetricians and Gynecologists in 2018 because of better live birth rates than with clomiphene
   2. Symptomatic improvement
      a. Hormonal contraceptives (estrogen/progestin combination): Endocrine Society first-line therapy for menstrual abnormalities, hirsutism, or acne
      b. Metformin
         i. Effective for metabolic and glycemic abnormalities, if present, but only modestly effective for hirsutism
         ii. Alternative to hormonal contraception for irregular menses when hormonal contraceptives are contraindicated
         iii. Few data to support use for increased fertility (may improve pregnancy rate but not shown to improve rates of live births)

c. Spironolactone
   i. Often added to hormonal contraceptives
   ii. Can help with hirsutism
d. Pioglitazone: Questionable whether benefits outweigh risks in PCOS. Not recommended in Endocrine Society guidelines

VI. DIABETES MELLITUS

A. Consensus Recommendations
1. American Diabetes Association (ADA). Updated yearly in the January supplement of Diabetes Care (www.diabetes.org)
2. American College of Endocrinology/AACE
3. Canadian Diabetes Association
4. Various European groups
5. For the remainder of this section, unless otherwise noted, the ADA recommendations will be followed.

B. Classification
1. T1D
   a. Attributable to cellular-mediated β-cell destruction leading to insulin deficiency (insulin needed for survival)
   b. Accounts for 5%–10% of DM
   c. Formerly known as *insulin-dependent diabetes* and *juvenile-onset diabetes*
   d. Usually presents in childhood or early adulthood but can present in any stage of life
   e. Usually symptomatic with a rapid onset in childhood, but a slower onset can occur in older adults
   f. The ADA now recommends a staging of patients with T1D based on the degree of dysglycemia and symptoms.
      i. Stage 1: Multiple autoantibodies present but glucose concentrations are normal
      ii. Stage 2: Multiple autoantibodies present, glucose concentrations consistent with prediabetes (see criteria in text that follows), and patient is asymptomatic
      iii. Stage 3: Symptomatic and glucose concentrations consistent with diabetes (see criteria in text that follows)
2. T2D
   a. Results primarily from insulin resistance in muscle and liver, with subsequent defect in pancreatic insulin secretion, though GI, brain, liver, and kidneys are all involved in the pathophysiology
   b. Accounts for 90%–95% of diabetes mellitus
   c. Formerly known as *non–insulin-dependent diabetes* or *adult-onset diabetes*
   d. Often asymptomatic, with a slow onset over 5–10 years. Rationale for early, frequent screening of those at risk (see text that follows) and initial assessment for complications at diagnosis
   e. Disturbing increased trends in T2D in children and adolescents attributed to rise in obesity
3. Maturity-onset diabetes of the young
   a. Result of genetic disorder leading to impaired secretion of insulin with little or no impairment in insulin action
   b. Onset usually before age 25 and can mimic T1D or T2D
   c. Often misdiagnosed for type 1 diabetes. Patients may respond to sulfonylurea therapy.
4. Gestational diabetes
   a. Glucose intolerance occurring during pregnancy
   b. Prevalence: 1%–14% of pregnancies (complicates about 4% of pregnancies)
   c. Most common in third trimester

5. Prediabetes
    a. Impaired glucose tolerance
    b. Impaired fasting glucose
6. Other DM types
    a. Genetic defects in β-cell function or insulin action
    b. Diseases of the pancreas (e.g., pancreatitis, neoplasia, cystic fibrosis)
    c. Drug or chemical induced (e.g., glucocorticoids, nicotinic acid, protease inhibitors, atypical antipsychotics)

Patient Case

6. A 64-year-old African American woman has had a 12-kg (27 lb) weight increase during the past year, primarily because of inactivity and a poor diet. Her BMI is 44 kg/m^2. Her mother and sister both have T2D. Her fasting glucose concentration today is 212 mg/dL. Which is the best course of action?

    A. Diagnose T2D and begin treatment.

    B. Diagnose T1D and begin treatment.

    C. Obtain another glucose concentration today.

    D. Obtain an A1C today in addition to the glucose concentration.

C. Screening for DM (using glycemic diagnostic criteria discussed in greater detail in the text that follows)
    1. T1D
        a. Symptomatic patients
        b. Asymptomatic patients at higher risk
            i. First-degree relatives with T1D
            ii. Measure islet autoantibodies to assess risk of T1D.
            iii. If screen is positive for antibodies, counsel on symptoms of hyperglycemia and risk of DM. Consider enrollment in observational study.
    2. T2D
        a. Age 45 or older, repeat every 3 years if normal
        b. Screen regardless of age if BMI is 25 kg/m^2 or greater (23 kg/m^2 or greater in Asian Americans) and at least one of the following risk factors:
            i. History of cardiovascular disease
            ii. A1C is 5.7% or greater, impaired glucose tolerance, or impaired fasting glucose in previous testing
            iii. History of PCOS
            iv. HDL less than 35 mg/dL or TG greater than 250 mg/dL
            v. Hypertension
            vi. High-risk ethnicity: African American, Latino, Native American, Asian American, Pacific Islander
            vii. First-degree relative with T2D
            viii. Physical inactivity
            ix. Insulin resistance conditions (e.g., severe obesity, acanthosis nigricans)
    3. Gestational DM
        a. Screen at first prenatal visit for undiagnosed T2D in all patients with T2D risk factors present.
        b. Screen at 24–28 weeks' gestation using OGTT.
        c. If a diagnosis of gestational DM is made, screen for diabetes 4–12 weeks after delivery.
        d. Continue to screen patients who have had gestational DM every 3 years for T2D for life.

D. DM Diagnosis
   1. T1D and T2D diagnosis
      a. Glycemic values in nonpregnant patients
         i. FPG
            (a) Easy, convenient
            (b) 126 mg/dL or greater
         ii. Random plasma glucose
            (a) 200 mg/dL or greater with symptoms of hyperglycemia
            (b) Common hyperglycemia symptoms include polyuria, polydipsia, and unexplained weight loss.
         iii. OGTT
            (a) Plasma glucose concentration obtained 2 hours after a 75-g oral glucose ingestion
            (b) 200 mg/dL or greater
            (c) More sensitive and specific than FPG but more cumbersome to perform
         iv. A1C (glycated hemoglobin)
            (a) 6.5% or greater
            (b) May be less sensitive than FPG in identifying mild diabetes, but does not require fasting and has less variability from day to day
            (c) A1C values may be inaccurate in patients with anemia, chronic malaria, sickle cell anemia, pregnancy, or significant blood loss or recent blood transfusion.
         v. The diagnosis of both T1D and T2D requires two abnormal tests showing hyperglycemia and can be obtained from the same sample (using two of the above criteria) or in two separate test samples (can be the same type of test).
      b. Other useful diagnostic tests if type of DM is in question
         i. C-peptide (measure of endogenous insulin secretion, usually negligible in T1D and normal or elevated early in T2D)
         ii. Presence of islet cell autoantibodies, autoantibodies to insulin, glutamic acid decarboxylase, or tyrosine phosphatase (all suggest autoimmune activity)
   2. Gestational diabetes diagnosis: Glycemic values in pregnancy
      a. Updated and simplified diagnostic criteria
      b. "One-step" approach: 75-g OGTT at 24–28 weeks' gestation
         i. Fasting: 92 mg/dL or greater
         ii. 1 hour after OGTT: 180 mg/dL or greater
         iii. 2 hours after OGTT: 153 mg/dL or greater
      c. "Two-step" approach: 50-g OGTT (nonfasting) at 24–28 weeks' gestation
         i. If 1 hour after 50-g OGTT is less than 140 mg/dL, no further workup
         ii. If 140 mg/dL or greater, do additional fasting OGTT using 100 g (see the ADA guidelines for diagnostic glucose criteria)
   3. Prediabetes diagnosis (high-risk population)
      a. Impaired fasting glucose: FPG 100–125 mg/dL
      b. Impaired glucose tolerance: 2-hour plasma glucose after OGTT (75 g) of 140–199 mg/dL
      c. A1C 5.7%–6.4%
      d. Screen yearly for T2D if positive for prediabetes

Patient Case

7. A 56-year-old man with T2D takes metformin 1000 mg twice daily. He has no other chronic diseases or history of cardiovascular disease. His current vital signs and laboratory results are as follows: blood pressure 148/78 mm Hg, heart rate 74 beats/minute, and A1C 6.9%. Which agent, if added to the current regimen, has the most potential to reduce both microvascular and macrovascular complications in this patient?

   A. Insulin glargine.

   B. Lisinopril.

   C. Glyburide.

   D. Niacin.

E. Goals of Diabetes Management in Nonpregnant Adults
   1. Primary goal: Prevent the onset of acute or chronic complications
   2. Acute complications: Hypoglycemia, diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar nonketotic syndrome
   3. Chronic complications
      a. Microvascular: Retinopathy, nephropathy, and neuropathy
      b. Macrovascular: Cardiovascular, cerebrovascular, and peripheral vascular diseases
   4. Glycemic therapy goals
      a. A1C less than 7.0% (Note: The American College of Endocrinology/AACE guidelines recommend 6.5% or less.)
         i. Obtain every 6 months in patients at goal A1C and every 3 months in those over goal.
         ii. Less-stringent A1C targets may be appropriate in those with a short life expectancy (e.g., terminal cancer), advanced diabetic complications, longstanding diabetes that is difficult to control (e.g., frail older adults with a history of hypoglycemia at risk of falls), or extensive other comorbidities (clinical atherosclerotic cardiovascular disease). (In such situations, a higher A1C [e.g., less than 8%] may be sufficient to limit the risk of acute complications of hyperglycemia such as dehydration and electrolyte deficiencies while preventing exacerbation of comorbidities.)
      b. FPG or premeal 80–130 mg/dL. Frequency of monitoring depends on regimen, type of DM, and current glycemic control.
      c. Peak postprandial glucose (1–2 hours after a meal) less than 180 mg/dL
   5. Non-glycemic therapy goals
      a. Blood pressure
         i. The ADA recommends a blood pressure goal of less than 130/80 mm Hg in patients at high risk of cardiovascular disease (existing cardiovascular disease or greater than a 15% ten-year risk) and a goal of less than 140/90 mm Hg in those at lower risk.
         ii. ACC/AHA hypertension guidelines recommend less than 130/80 mm Hg.
      b. Lipids
         i. ADA: No specific LDL goal is currently recommended.
         ii. ACC/AHA 2018 guidelines suggest lowering LDL by 30%–49% in patients with diabetes age 40–75 and by at least 50% if at higher risk, e.g. age 50-75 or patient has other risk factors.
         iii. No specific TG or HDL goals are currently recommended.

F. Goals for Gestational Diabetes
   1. Primary goal: Prevent complications to mother and child.
   2. Glycemic therapy goals (more stringent)
      a. FPG of 95 mg/dL or less
      b. 1-hour postprandial glucose 140 mg/dL or less
      c. 2-hour postprandial glucose 120 mg/dL or less
   3. Potential complications of hyperglycemia during pregnancy
      a. Mother: Hypertension, preeclampsia, T2D after pregnancy
      b. Fetus/child: Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome

G. Benefits of Optimizing Diabetes Management in Nonpregnant Adults
   1. Glycemic control
      a. Reduces the risk of developing retinopathy, nephropathy, and neuropathy in T1D and T2D
      b. Prospective studies, specifically designed to assess optimizing glycemic control and effect on cardiovascular events, have shown little or no reduction in cardiovascular outcomes.
      c. However, the "legacy" effect in the Diabetes Control and Complications Trial of T1D and the UK Prospective Diabetes Study of T2D suggests early control has future cardiovascular benefit.
      d. No profound benefit of aggressive glycemic control in T2D (A1C less than 6.5%)
   2. Blood pressure control: Reduction in both macrovascular and microvascular complications
   3. Lipid control: Reduction in LDL with moderate-intensity statin therapy reduces cardiovascular complications.

Patient Case

8. A 21-year-old patient (weight 80 kg) is given a diagnosis of T1D after the discovery of elevated glucose concentrations (average 326 mg/dL), and the patient has signs and symptoms of hyperglycemia. Which is the most appropriate initial dose of rapid-acting insulin before breakfast for this patient? (Assume a TDI regimen of 0.5 unit/kg/day.)

   A. 2 units.

   B. 4 units.

   C. 7 units.

   D. 14 units.

H. Therapeutic Management of T1D (Table 3)
   1. Insulin agents
      a. Categorized on the basis of duration after injection
         i. Rapid acting: Insulin aspart (two formulations), lispro, glulisine, and inhaled insulin
         ii. Short acting: Regular human insulin
         iii. Intermediate acting: Neutral protamine Hagedorn (NPH)
         iv. Long acting: Insulin glargine, degludec and detemir
      b. Combination insulin products (intermediate or long acting, regular or rapid acting): 70/30, 75/25, insulin degludec and glargine available in combination with GLP-1 agonist
      c. Higher-concentration insulin products
         i. More commonly used in patients with T2D needing significant daily insulin doses
         ii. U-300 glargine (300 units/mL), U-200 degludec (200 units/mL), U-200 lispro (200 units/mL), U-500 regular insulin (500 units/mL)

Table 3. Characteristics of U-100 (100 units/mL) Insulins[a]

Category	Drug Name	Clarity	Onset	Administration Time Before Meal (min)	Peak (hr)	Duration (hr)
Rapid acting	Aspart Lispro Glulisine Inhaled insulin	Clear	15–30 min	15 (inhaled insulin at beginning of meal)	1–3 (shorter with inhaled and fast-acting aspart/lispro)	2–5 (shorter with inhaled and fast-acting aspart/lispro)
Short acting	Regular	Clear	30–60 min	30	2–3	4–6
Intermediate acting	Neutral protamine Hagedorn	Cloudy	1–2 hr	N/A	4–8	10–20
Long acting	Detemir Glargine Degludec	Clear	2–4 hr 1–2 hr 1–2 hr	N/A	6–8 "Peakless" "Peakless"	6–24 ~24 24–42

[a]The times given depend on the source of data and intersubject variability.

N/A = not applicable.

   d. Glycemic target
      i. Regular- and short-acting insulins target postprandial glucose concentrations.
      ii. Intermediate- and long-acting insulins target fasting glucose concentrations.
   e. Inhaled insulin may cause bronchospasm and is contraindicated in patients with asthma, chronic obstructive pulmonary disease, or lung cancer. Requires spirometry testing at baseline, at 6 months of therapy, and annually thereafter

2. Management of insulin therapy
   a. First step is to estimate TDI requirements.
   b. Weight-based estimate if insulin naive
      i. 0.3–0.6 unit/kg/day
      ii. Requirements higher if treating DKA near initial diagnosis of DM
      iii. Honeymoon phase shortly after treatment initiation often requires lower daily insulin needs.
   c. With older insulin formulations (NPH and regular insulin)
      i. Two-thirds of TDI is given before the morning meal. Two-thirds of this is given as NPH, and one-third is given as regular insulin.
      ii. One-third of TDI is given before the evening meal. Either with two-thirds given as NPH and one-third given as regular insulin or in a 1:1 ratio. Alternative is regular given before evening meal and NPH at bedtime.
      iii. Advantages: Daily insulin injection frequency two or three times daily and less expensive than newer insulins
      iv. Disadvantages: Does not mimic natural insulin secretion pattern; prone to hypoglycemic events
   d. Basal-bolus insulin therapy (i.e., physiologic insulin therapy)
      i. Use insulin analogs to better mimic natural insulin secretion patterns
      ii. Use long-acting basal insulin to prevent ketosis and control FPG
      iii. Use bolus insulin to control postprandial hyperglycemia
      iv. Basal insulins: Insulin glargine or degludec once daily or insulin detemir once or twice daily
      v. Bolus insulins: Rapid-acting insulin (can use short-acting insulin)
      vi. Basal requirements are typically 50% of estimated TDI, but some practitioners may prefer more or less.

vii. Bolus requirements are typically 50% of estimated TDI split three ways before meals.
(a) Provides initial estimate of prandial insulin needs
(b) Typically, patients begin to estimate bolus requirements given the amount of carbohydrates to be ingested. Requires significant patient education in food carbohydrate estimates
(c) Alternative bolus requirement (Rule of 500): Dividing 500 by TDI will estimate the amount of carbohydrates (in grams) that 1 unit of a rapid-acting insulin will cover.
viii. Advantages over NPH plus regular approach: More physiologic, less hypoglycemia, more flexible to patient mealtimes
ix. Disadvantages: Cost and increased frequency and number of daily injections (rapid-acting and basal insulin must be injected separately). Note that the same process of basal-bolus insulin therapy can apply to a patient with T2D who is receiving intensive insulin therapy with or without oral DM medications.

e. Correctional insulin needs
i. Always a need to correct for hyperglycemic excursions, despite optimal basal-bolus therapy
ii. "1800 rule": 1800/TDI = milligrams per deciliter of glucose lowering per 1 unit of rapid-acting insulin
(a) For example, if TDI is 60 units, 1800/60 = 30, suggesting that 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.
(b) Also called *insulin sensitivity factor*
(c) Alternative: "1500 rule" when using regular human insulin (i.e., 1500/TDI)
iii. More patient-specific than traditional sliding-scale insulin

f. Continuous glucose monitoring (CGM)
i. Used with or without insulin pumps
ii. Real-time CGM (continuously transmits glucose data to sensor or smart device)
iii. Intermittent CGM (requires scanning by a sensor to view glucose data)

g. Continuous subcutaneous insulin infusion (insulin pump)
i. Device allows patient-specific hourly basal dosing and bolus insulin dosing.
ii. Uses rapid-acting insulins
iii. Requires patient education and carbohydrate counting
iv. Used in conjunction with continuous glucose monitoring devices. Technology is rapidly advancing (newest systems, called "hybrid closed-loop systems," act almost as an artificial pancreas).

h. Assessing therapy and dosage adjustment
i. Know the goals for fasting and postprandial glucose concentrations.
ii. Identify when patient is at goal and not at goal (hypoglycemia or hyperglycemia). Look for consistent trends rather than isolated events.
iii. Identify which insulin affects problematic glucose concentrations.
iv. Adjust insulin dosage or patient behavior accordingly.
v. Same process for treating T2D applies (see text that follows)

3. Amylin analog
a. Mechanism of action: Amylin is cosecreted with insulin and has effects similar to those of GLP-1 described in the text that follows.
b. Pramlintide is currently the only agent in this class available in the United States. Pramlintide can be used in either T1D or T2D as adjunctive therapy in patients receiving insulin.

c. Dosing
   i. T1D
      (a) Initial: 15 mcg subcutaneously immediately before main meals
      (b) Must reduce dosage of preprandial rapid-acting, short-acting, or combination insulin products by 50%
      (c) Maximal daily dosage is 60 mcg with each meal.
      (d) Dosage should be titrated in 15-mcg increments, as tolerated, but no more rapidly than every 3 days.
   ii. T2D
      (a) Initial: 60 mcg subcutaneously immediately before main meals
      (b) Must reduce preprandial insulins by 50%
      (c) Maximal daily dosage: 120 mcg with each meal
      (d) Dosage should be titrated in 60-mcg increments, as tolerated, but no more rapidly than every 3–7 days.
   iii. Use of prefilled pens is strongly recommended, when possible, rather than a syringe and vial, to reduce the risk of dosing errors (dosing instructions with U-100 syringes and vial in package insert).
   iv. Cannot be mixed with insulin products; requires increased frequency of daily injections
d. Adverse effects
   i. Boxed warning for severe hypoglycemia, especially in patients with T1D
   ii. Nausea, vomiting, anorexia, headache
e. Contraindications and precautions
   i. Substantial gastroparesis
   ii. History of poor adherence or monitoring of BG
   iii. A1C greater than 9%
   iv. Hypoglycemia unawareness or frequent bouts of hypoglycemia
f. Efficacy
   i. A 0.5%–1% reduction in A1C
   ii. Effective at controlling postprandial glucose excursions

Patient Cases

9. A 55-year-old man with T2D for 6 months has been receiving metformin 1000 mg twice daily since his diagnosis. His A1C today is 8.2%. His morning fasting blood glucose (FBG) readings are consistently at goal. His after-meal glucose readings average 210–230 mg/dL. The patient states that he is worried about his weight and does not want to add a medication that might increase it. Which would be most appropriate for this patient?

   A. Glyburide.

   B. Liraglutide.

   C. Pioglitazone.

   D. Insulin glargine.

10. A 66-year-old man has had T2D for 4 years. His A1C today is 7.7%. He has altered his diet and states that he has been exercising regularly for months. He takes metformin 1000 mg twice daily. Which would best help optimize his glycemic control?

   A. Continue current medications and counsel to improve his diet and exercise.

   B. Discontinue metformin and initiate exenatide 5 mcg twice daily.

   C. Add bromocriptine 0.8 mg at bedtime.

   D. Add sitagliptin 100 mg once daily to his metformin therapy.

I. Therapeutic Management of T2D
   1. Given the progressive nature of T2D, a stepwise approach is usually needed.
   2. ADA treatment recommendations for hyperglycemia emphasize a patient-centered approach to care, considering patient preferences, needs, and values.
   3. Metformin remains the initial drug of choice, unless contraindicated or adverse effects preclude its use or if improvements in exercise and diet early after diagnosis fail to control hyperglycemia. (Consider combination therapy of metformin with the medications listed in the text that follows if baseline A1C is 1.5% or greater above personal goal A1C.)
   4. If metformin monotherapy fails to allow the patient to attain or maintain glycemic control, adding other agents is based on several criteria and weighs the advantages and disadvantages of the various oral and injectable agents.
      a. Efficacy in lowering A1C (also focus on ability to lower fasting or postprandial glucose concentrations or both)
      b. Existing comorbidities
         i. Cardiovascular disease: Consider GLP-1 agonist or SGLT-2 inhibitor
         ii. Heart failure or chronic kidney disease: Consider SGLT-2 inhibitor
      c. Risk of hypoglycemia
      d. Effects on weight
      e. Adverse effect profile
      f. Cost
      g. Oral or injection patient preference
   5. Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors, GLP-1 agonists, and basal insulin are preferred to less efficacious options or agents with a higher adverse risk profile.
   6. Adding injectable medications to existing oral DM agents
      a. ADA recommends GLP-1 agonists as preferred to insulin unless extreme or symptomatic hyperglycemia is present.
         i. Because of a mildly improved A1C reduction with GLP-1 agonists compared with insulin therapies
         ii. GLP-1 agonists have a lower risk of hypoglycemia and are associated with weight loss.
      b. Consider addition of a basal insulin / GLP-1 agonist combination or basal/bolus insulin regimen when significant hyperglycemia exists. 2018 ADA updated report suggests adding either early in therapy if:
         i. A1C greater than 10% or
         ii. A1C is greater than 2% above goal
      c. Weight-based dosing: For example, 0.1–0.2 unit/kg/day of basal insulin (higher dosages if significant hyperglycemia exists)
      d. Can increase basal insulin according to fasting glucose concentrations
      e. Can add GLP-1 agonist or SGLT-2 inhibitor if weight gain is a concern or bolus insulin to one or more meals if postprandial glucose is a concern after initiating basal insulin
      f. Insulin secretagogues should be lowered in dosage or discontinued altogether when bolus insulin added to reduce risk of hypoglycemia
      g. Thiazolidinediones should be lowered or discontinued when basal or bolus insulin is added to the regimen because of the increased risk of edema.
   7. Changing from oral DM medications to insulin-only management (e.g., because of adverse effects, contraindications, lack of efficacy of oral medications)
      a. Can follow NPH/regular insulin or basal-bolus approach similar to that in T1D described earlier
      b. The TDI requirements in T2D are usually much higher than in T1D because of insulin resistance.

J. Therapeutic Agents in T2D
   1. Metformin (biguanide)
      a. Mechanism of action: Reduces hepatic gluconeogenesis; also favorably affects insulin sensitivity and, to a lesser extent, intestinal absorption of glucose
      b. Dosing
         i. Initial: 500 mg once or twice daily (once daily with extended-release formulation)
         ii. Maximal daily dose: 2550 mg (more commonly, 2000 mg/day)
         iii. Can increase at weekly intervals as necessary
         iv. Small initial dosage and slow titration secondary to GI disturbances
      c. Adverse effects
         i. Common: Nausea, vomiting, diarrhea, epigastric pain
         ii. Less common: Decrease in vitamin B_{12} concentrations (monitor periodically), lactic acidosis (rare)
         iii. Signs or symptoms of lactic acidosis include acidosis, nausea, vomiting, increased respiratory rate, abdominal pain, shock, and tachycardia.
      d. Contraindications and precautions (because of risk of lactic acidosis)
         i. Renal impairment (contraindicated because of increased risk of lactic acidosis)
            (a) Historically contraindicated if SCr 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women or reduced creatinine clearance (CrCl)
            (b) In 2016, the FDA suggested that eGFR be used as a measure of kidney function rather than creatinine alone. Discontinue if eGFR is less than 30 mL/minute/1.73 m^2, and initiating if eGFR is 30–45 mL/minute/1.73 m^2 is not recommended. Assess benefit of continuing use in patients already prescribed metformin if eGFR is 30–45 mL/minute/1.73 m^2 and consider a 50% dose reduction.
            (c) Monitor renal function every 3–6 months in patients with eGFR of 45–60 mL/minute/1.73 m^2 and every 3 months if 30–45 mL/minute/1.73 m^2
         ii. Age 80 or older (use caution and carefully assess renal function)
         iii. High risk of cardiovascular event or hypoxic state
         iv. Hepatic impairment
         v. Interrupt therapy in patients with eGFR of 30–60 mL/minute/1.73 m^2 if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal SCr concentrations are achieved.
      e. Efficacy
         i. 1%–2% A1C reduction
         ii. Some benefit in TG reduction and weight loss
         iii. Considered first-line therapy unless contraindicated on the basis of adverse effect profile, reduction in A1C, cost, and limited data that it reduces cardiovascular events in overweight patients
   2. Sulfonylureas
      a. Mechanism of action: Bind to receptors on pancreatic β-cells, leading to membrane depolarization, with subsequent stimulation of insulin secretion (insulin secretagogue)
      b. First-generation agents seldom used today (e.g., chlorpropamide, tolbutamide)
      c. Second-generation agents (e.g., glyburide, glipizide, glimepiride). Dosage titration: Can increase at weekly intervals, as necessary
      d. Adverse effects
         i. Common: Hypoglycemia, weight gain
         ii. Less common: Rash, headache, nausea, vomiting, photosensitivity
         iii. Rare: Lactic acidosis

e. Contraindications and precautions
   i. Hypersensitivity to sulfonamides
   ii. Patients with hypoglycemic unawareness
   iii. Poor renal function (glipizide may be a better option than glyburide or glimepiride in older adults or in those with renal impairment because drug or active metabolites are not renally eliminated)
f. Efficacy
   i. 1%–2% A1C reduction
   ii. Note: For this and all medications used to treat hyperglycemia, the absolute decrease in A1C is larger for higher baseline A1C values and smaller for lower A1C values.

Table 4. Second-Generation Sulfonylurea Dosing Strategies

Drug	Initial Dosage	Maximum Daily Dosage (mg)
Glyburide (not micronized)	2.5–5.0 mg once or twice daily	20
Glyburide (micronized)	1.5–3 mg once or twice daily	12
Glipizide	5 mg once or twice daily (once daily with extended release)	40 (little improved efficacy > 20 mg/day)
Glimepiride	1–2 mg once daily	8

3. Meglitinides
   a. Mechanism of action: Similar to that of sulfonylureas in increasing insulin secretion from the pancreas, but with a more rapid onset and shorter duration of activity
   b. Glucose-dependent activity
   c. Two currently available: Repaglinide and nateglinide
   d. Dosing
      i. Repaglinide
         (a) Initial: 0.5–1 mg 15 minutes before meals
         (b) Maximal daily dosage: 16 mg
      ii. Nateglinide
         (a) 120 mg before meals
         (b) 60 mg if A1C near goal
      iii. Repaglinide can be increased in weekly intervals, if needed.
   e. Adverse effects: Hypoglycemia (though less than with sulfonylureas), weight gain, upper respiratory infection
   f. Contraindications and precautions
      i. Hypersensitivity
      ii. Caution in concomitant use of repaglinide and gemfibrozil: Can lead to greatly increased repaglinide concentrations
   g. Efficacy
      i. 0.5%–1.5% A1C reduction (repaglinide reduces A1C more than nateglinide)
      ii. Most effective on postprandial glucose excursions
4. Thiazolidinediones (often called *glitazones* or *TZDs*)
   a. Mechanism of action
      i. Peroxisome proliferator–activated receptor γ-agonist
      ii. Increases expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity

b. Two agents available: Pioglitazone and rosiglitazone
    i. In September 2010, the FDA initiated restricted access to rosiglitazone because of continued concerns about its cardiovascular safety. Rosiglitazone was restricted to patients who are unable to attain glycemic control with other agents and when pioglitazone is not used for medical reasons.
    ii. In November 2013, the FDA removed some prescribing and dispensing restrictions for rosiglitazone after evaluating clinical trial data.
c. Dosing
    i. Pioglitazone
        (a) Initial: 15 mg once daily
        (b) Maximal daily dosage: 45 mg
    ii. Dosage titration is slow, and the maximal effect of a dosage change may not be observed for 8–12 weeks.
d. Adverse effects
    i. Weight gain
    ii. Fluid retention (particularly peripheral edema) is worse with insulin use and is dose-dependent. Edema is less responsive to diuretic therapy. Macular edema can result.
    iii. Risk of proximal bone fractures; use caution in patients with existing osteopenia or osteoporosis (discontinuation reduces risk)
    iv. Possible risk of bladder cancer with pioglitazone (dosage and duration of use dependent). Data are contradictory.
    v. Increased risk of heart failure
        (a) Boxed warning
        (b) More than a 2-fold higher relative risk, although absolute risk is quite small
    vi. Both agents have been withdrawn from some countries in Europe.
e. Contraindications and precautions
    i. Hepatic impairment
    ii. Class III/IV heart failure (symptomatic heart failure)
    iii. Existing fluid retention
f. Efficacy
    i. 0.5%–1.4% A1C reduction
    ii. Both drugs increase HDL, but pioglitazone has a more favorable effect in reducing LDL and TG than does rosiglitazone.

5. DPP-4 inhibitors
    a. Mechanism of action: Inhibit the breakdown of GLP-1 secreted during meals, which in turn increases pancreatic insulin secretion, limits glucagon secretion, slows gastric emptying, and promotes satiety
    b. Dosing
        i. Sitagliptin: 100 mg once daily
            (a) Reduce dosage with CrCl if 30–49 mL/minute/or greater to 50 mg once daily.
            (b) Reduce dosage with CrCl less than 30 mL/minute to 25 mg once daily.
        ii. Saxagliptin: 5 mg once daily
            (a) Reduce dosage with CrCl of 50 mL/minute or less to 2.5 mg once daily.
            (b) Reduce dosage when coadministered with strong CYP3A4/5 inhibitor (e.g., ketoconazole) to 2.5 mg once daily.
        iii. Linagliptin: 5 mg once daily (no dosage adjustment for renal impairment)
        iv. Alogliptin: 25 mg once daily
            (a) Reduce dosage with CrCl of 30–59 mL/minute to 12.5 mg once daily.
            (b) Reduce dosage with CrCl less than 30 mL/minute to 6.25 mg once daily.

c. Adverse effects
   i. Upper respiratory and urinary tract infections, headache, severe joint pain
   ii. Hypoglycemia with monotherapy is minimal, but frequency is increased with concurrent sulfonylurea therapy (can lower dosage of sulfonylurea when initiating).
   iii. Sitagliptin has had some postmarketing reports of acute pancreatitis, angioedema, Stevens-Johnson syndrome, and anaphylaxis.
   iv. Safety studies of saxagliptin and, to a lesser extent, alogliptin (but not sitagliptin or linagliptin) have shown an increased risk of heart failure hospitalization. In 2017, the FDA recommended warnings to package labeling of all DPP-4 inhibitors.
d. Contraindications and precautions
   i. Previous hypersensitivity to the agents
   ii. History of pancreatitis
e. Efficacy: 0.5%–0.8% reduction in A1C, considered weight neutral

6. SGLT-2 inhibitor
   a. Mechanism of action: Increases urinary glucose excretion by blocking normal reabsorption in the proximal convoluted tubule; has some effect on delaying GI glucose absorption
   b. Dosing
      i. Canagliflozin
         (a) 100 mg once daily before the first meal of the day
         (b) Maximal daily dosage: 300 mg
         (c) Reduce dosage with eGFR of 30–59 mL/minute/1.73 m^2 to 100 mg daily.
         (d) Discontinue or do not initiate if eGFR is less than 30 mL/minute/1.73 m^2.
      ii. Dapagliflozin
         (a) 5 mg once daily in the morning (with or without food)
         (b) Maximal daily dosage: 10 mg
         (c) Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m^2.
      iii. Empagliflozin
         (a) 10 mg once daily in the morning (with or without food)
         (b) Maximal daily dosage: 25 mg
         (c) Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m^2.
      iv. Ertugliflozin
         (a) 5 mg once daily in the morning (with or without food)
         (b) Maximal daily dosage: 15 mg
         (c) Discontinue or do not initiate if eGFR is less than 60 mL/minute/1.73 m^2.
   c. Adverse effects
      i. Increased urination
      ii. Urinary tract infections (in 2016, the FDA strengthened warning in product labeling for dapagliflozin and canagliflozin)
      iii. Genital mycotic infections (more common in females)
      iv. Hypotension
      v. Increased hypoglycemia risk with concomitant insulin or insulin secretagogue
      vi. Class is linked with rare cases of euglycemic DKA and Fournier gangrene.
      vii. Possible increased bone fracture risk, decreased bone mineral density, and foot or leg amputation with canagliflozin

d. Contraindications and precautions
   i. Significant renal impairment (varies by agent, as stated earlier)
   ii. Suggested to ensure euvolemia before initiating agent, given its diuretic effect especially in older adults, patients with existing renal impairment or already low blood pressure, or patients receiving diuretics
   iii. Consider factors that could predispose the patient to acute kidney injury (e.g., low blood volume, chronic kidney insufficiency, heart failure, or medications that could alter kidney function).
   iv. Agent should be discontinued before any surgery to reduce the risk of ketoacidosis (3 days before with canagliflozin, dapagliflozin, and empagliflozin and 4 days before with ertugliflozin).
e. Efficacy
   i. 0.3%–1.0% reduction in A1C
   ii. Effect on both fasting and postprandial glucose concentrations
   iii. Mild weight loss
   iv. Empagliflozin, dapagliflozin, and canagliflozin can reduce cardiovascular morbidity in patients with T2D and established cardiovascular disease and may improve renal outcomes. Canagliflozin in patients with significant urine albumin excretion and renal insufficiency reduces the risk of end-stage renal disease, doubling of SCr, or renal death.

Patient Case

11. A 66-year-old man is given a diagnosis today of T2D. Two weeks ago, his A1C was 7.5% and SCr was 1.8 mg/dL (eGFR 25 mL/minute/1.73 m^2). He has a history of hypertension, dyslipidemia, and systolic heart failure (New York Heart Association class III, ejection fraction 33%). He has 2+ pitting edema bilaterally. In addition to improvements in diet and exercise, which is best to initiate?

    A. Linagliptin.

    B. Pioglitazone.

    C. Exenatide.

    D. Metformin.

7. GLP-1 analogs
   a. Mechanism of action: Synthetic analog of human GLP-1 that binds to GLP-1 receptors, resulting in glucose-dependent insulin secretion, reduction in glucagon secretion, and reduced gastric emptying; promotes satiety
   b. Approved agents: Exenatide, liraglutide, dulaglutide, lixisenatide, and semaglutide
   c. Dosing
      i. Exenatide
         (a) Twice-daily formulation (pen)
            (1) Initial: 5 mcg subcutaneously twice daily, administered no more than 60 minutes before morning and evening meals
            (2) Maximal dosage: 10 mcg twice daily
            (3) Dosage titration from 5 mcg to 10 mcg twice daily after 1 month, if tolerated
         (b) Once-weekly formulation (single-dose tray or pen, each containing lyophilized powder and diluent)
            (1) 2 mg subcutaneously once weekly
            (2) Powder must be reconstituted by patient immediately before injection.

ii. Liraglutide (pen)
(a) 0.6 mg subcutaneously once daily for 1 week (regardless of mealtime)
(b) Dosage titration from 0.6 to 1.2 mg/day, if tolerated
(c) Maximal daily dosage: 1.8 mg/day
iii. Lixisenatide (pen)
(a) Initial dose: 10 mcg once daily for 14 days
(b) Maintenance dose: 20 mcg once daily
iv. Dulaglutide (pen and single-dose syringe)
(a) 0.75 mg subcutaneously once weekly
(b) Dosage titration to 4.5 mg once weekly for additional glycemic control
v. Semaglutide (pen and single-dose syringe and oral formulation)
(a) 0.25 mg subcutaneously once weekly
(b) Dosage titration to 1 mg once weekly at monthly intervals for additional glycemic control
(c) Oral formulation is dosed starting with 3 mg once daily and increased at monthly intervals to a maximum dose of 14 mg daily.

d. Adverse effects
i. Nausea, vomiting, diarrhea common, but can subside or cease over time
ii. Hypoglycemia common with concurrent sulfonylurea (consider reduction in sulfonylurea dose)
iii. Postmarketing reports of pancreatitis and acute renal failure or impairment

e. Contraindications and precautions
i. Impaired renal function: CrCl less than 30 mL/minute for either exenatide formulation; less specific for liraglutide. No dose adjustment necessary with semaglutide
ii. Caution with a history of severe GI tract disorder, particularly gastroparesis
iii. History of pancreatitis
iv. For liraglutide, semaglutide, dulaglutide, once-weekly exenatide: Contraindicated in patients with a personal or family history of medullary thyroid carcinoma (adverse effect found in rodent studies but not in humans)

f. Efficacy
i. A 0.5%–1.5% reduction in A1C
ii. Effects on postprandial hyperglycemia better than on fasting glucose concentrations with once- or twice-daily formulations
iii. Improved A1C, fasting glucose reduction, and nausea or vomiting with once-weekly than with twice-daily exenatide formulation
iv. Modest weight loss
v. Liraglutide, dulaglutide, exenatide, and semaglutide have been shown to reduce some cardiovascular outcomes in high-risk patients, whereas lixisenatide has not, question whether class effect because populations studied in cardiovascular outcomes trials differed greatly with respect to percentages of those with existing cardiovascular disease

8. α-Glucosidase inhibitors
a. Mechanism of action: Slows the absorption of glucose from the intestine to the bloodstream by slowing the breakdown of large carbohydrates into smaller absorbable sugars
b. Two agents available: Acarbose and miglitol
c. Dosing (both agents dosed similarly)
i. Initial: 25 mg three times daily at each meal
ii. Maximum daily dosage: 300 mg
iii. Slow titration, increasing as tolerated every 4–8 weeks to minimize GI adverse effects

d. Adverse effects
    i. Flatulence, diarrhea, abdominal pain
    ii. Increased liver enzymes with high doses of acarbose
e. Contraindications and precautions: Inflammatory bowel disease, colonic ulcerations, intestinal obstruction
f. Efficacy
    i. 0.5%–0.8% reduction in A1C, also shown to decrease body weight
    ii. Targets postprandial glucose excursions
    iii. Might not be as effective in patients using low-carbohydrate diets

9. Bile acid sequestrant:
    a. Mechanism of action
        i. Bile acid sequestrant used primarily for cholesterol management. Its mechanism to reduce serum glucose concentrations is not clearly understood. Colesevelam is thought to be an antagonist to the farnesoid X receptor, which subsequently reduces hepatic gluconeogenesis. By reducing bile acid absorption, colesevelam reduces farnesoid X receptor activity.
        ii. Used in conjunction with insulin or oral DM medications
    b. Colesevelam is the only studied and approved drug in this class.
    c. Dosing: Six 625-mg tablets once daily or three 625-mg tablets twice daily
    d. Adverse effects: Constipation, dyspepsia, nausea, myalgia
    e. Contraindications and precautions
        i. Contraindicated in patients with a history of bowel obstruction or serum triglyceride concentrations greater than 500 mg/dL
        ii. Caution in patients with swallowing disorders (large pill), dysphasia, gastric mobility disorders, and serum triglyceride concentrations greater than 300 mg/dL
    f. Efficacy: 0.3%–0.5% reduction in A1C
10. Bromocriptine
    a. Mechanism of action: Not clearly understood. Agonist for dopamine receptor D_2 is thought to reset circadian rhythm, which can reduce caloric intake and storage. Other effects may be through α_1-antagonism, α_2-agonistic properties, and modulation of serotonin and prolactin.
    b. Dosing
        i. Initial: 0.8 mg once daily on waking; take with food (increases bioavailability)
        ii. Maximal daily dosage: 4.8 mg
        iii. Titrate weekly by 0.8 mg/day as tolerated and according to response.
        iv. Tablet strength differs from generic formulations currently on the market.
    c. Adverse effects: Nausea, somnolence, fatigue, dizziness, vomiting, headache, orthostatic hypotension, syncope
    d. Contraindications and precautions
        i. Can limit the effectiveness of agents used to treat psychosis or exacerbate psychotic disorders
        ii. Should not be used in nursing mothers or patients with syncopal migraines
        iii. Concomitant use with dopamine antagonists (e.g., neuroleptic agents) can limit the efficacy of both agents.
    e. Efficacy (Table 5)
        i. 0.1%–0.6% reduction in A1C
        ii. Possible cardiovascular benefit

Table 5. Comparison of Therapies for Type 2 Diabetes Hyperglycemia Added to Metformin

Agent or Class	Primary Glycemic Effect	Benefits	Limitations and Precautions
Sulfonylurea	Fasting and prandial	Efficacy Cost	Weight gain Hypoglycemia risk Hastens β cell dysfunction
Meglitinide	Prandial	Prandial focus Use in kidney impairment	Hypoglycemia risk Weight gain Mealtime dosing
Pioglitazone	Fasting and prandial	Improved insulin sensitivity and pancreatic function Low risk of hypoglycemia Possible cardiovascular benefit Cost	Weight gain and edema Risk of heart failure Risk of osteoporosis Possible bladder cancer risk?
α-Glucosidase inhibitor	Prandial	No systemic absorption Prandial focus Weight loss	GI adverse effect profile Mealtime dosing Modest A1C effect
DPP-4 inhibitor	Prandial	Well tolerated Weight neutral	Possible pancreatitis risk? Modest A1C effect Possible increased heart failure risk (saxagliptin) Cost
GLP-1 agonist	Once- or twice-daily formulations have prandial focus Once-weekly formulations affect both fasting and prandial	Greater effect on prandial glucose Weight loss Efficacy Improves pancreatic function? Cardiovascular benefit (liraglutide, semaglutide, dulaglutide, and exenatide)	Nausea and vomiting Injection-site effects Questionable pancreatitis or thyroid cancer risk? Cost
Colesevelam	Prandial	Lipid benefits No systemic absorption	Large pill size and burden GI adverse effect profile Small decrease in A1C Avoid with high TG
Bromocriptine	Fasting and prandial	Low risk of hypoglycemia Possible cardiovascular benefit	Small decrease in A1C Central nervous system adverse effects
SGLT-2 inhibitors	Fasting and prandial	Low risk of hypoglycemia Efficacy Weight loss Possible heart failure, cardiovascular, and renal benefit	Urinary tract and genital infections Diuresis Euglycemic DKA?
Amylin agonist	Prandial	Modest weight loss Efficacy on postprandial glucose	High risk of hypoglycemia Must be taken with insulin Frequent injections Injection-site effects GI adverse effects
Insulin	Basal: Fasting Bolus: Prandial	Significant A1C reduction Flexibility in dosing strategies and titration	Hypoglycemia Weight gain Injection-site effects

DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP = glucagon-like peptide; SGLT = sodium glucose cotransporter.

Information adapted from: Davies M, D'Alessio D, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701; Garber A, Abrahamson M, Barzilay J, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2018 executive summary. Endocr Pract 2018;24:91-120.

K. Treatment of Inpatient DM (non–critically ill population)
   1. Joint guidelines from the ADA and AACE. The Endocrine Society also has guidelines.
   2. Strong association between admission hyperglycemia and worse inpatient outcomes and length of stay. Outcomes are worse in those who have stress-related hyperglycemia or are not known to have diabetes previously.
   3. Glycemic goals
      a. Less than 140 mg/dL fasting or premeal
      b. Less than 180 mg/dL random glucose
   4. Treatment
      a. Assess glucose concentrations before meals and at bedtime, if eating (every 4–6 hours if taking nothing by mouth [NPO]).
      b. Threshold for initiating therapy is 180 mg/dL or greater.
      c. According to the guidelines, subcutaneous insulin administration is the most practical way to improve hyperglycemia.
      d. Oral diabetes agents are generally not recommended unless the patient is clinically stable and eating regularly, and no significant precautions or contraindications for their use exist.
      e. Use of sliding-scale insulin alone is not recommended.
      f. Basal-bolus insulin therapy as described earlier in the treatment of T1D is recommended unless the patient is NPO. If NPO, use basal insulin alone

VII. TREATMENT OF DIABETES MELLITUS COMPLICATIONS

Patient Case

12. A patient with newly diagnosed T2D is screened for diabetic nephropathy. The following laboratory values are obtained today: blood pressure 129/78 mm Hg, heart rate 78 beats/minute, urine albumin/creatinine 27 mg/g, and estimated CrCl 94 mL/minute/1.73 m^2. Which would be the most appropriate treatment strategy?
    A. No change in therapy is warranted.
    B. Add an angiotensin-converting enzyme (ACE) inhibitor.
    C. Add a thiazide-like diuretic.
    D. Reduce daily protein intake.

A. Hypoglycemia
   1. Degree of intervention depends on glucose concentrations and presence of symptoms.
   2. Symptoms are patient-specific but can include anxiousness, sweating, nausea, tachycardia, hunger, and clammy skin.
   3. Consequences of significant hypoglycemia are most worrisome in the very young, older adults, and those with established heart disease.
   4. Classification (according to ADA recommendations)
      a. Level 1: Plasma glucose of 70 mg/dL or less with or without symptoms
      b. Level 2: Clinically significant hypoglycemia: Plasma glucose less than 54 mg/dL
      c. Level 3: A severe event characterized by altered mental and/or physical status requiring assistance

5. Treatment
    a. Mild to moderate hypoglycemia
        i. Oral ingestion of 15–20 g of glucose or equivalent
        ii. Repeat glucose concentration in 15 minutes and, if still less than 70 mg/dL, repeat ingestion of glucose.
        iii. Once glucose is normalized, ingest snack or meal.
    b. Clinically significant hypoglycemia (altered consciousness, needs assistance from others)
        i. Glucagon 1 mg subcutaneously or intramuscularly or 3 mg by nasal inhalation
        ii. Intravenous dextrose if patient does not respond to glucagon
        iii. Raise glucose targets for several weeks.

B. Diabetic Ketoacidosis
1. More common in T1D but can occur in T2D
2. Usually occurs because of a precipitating factor that stresses the body, resulting in increased counter-regulatory hormones
    a. Inappropriate (including nonadherence) or inadequate insulin therapy and infection are the two most common causes.
    b. Other causes: Myocardial infarction, pancreatitis, stroke, drugs (e.g., corticosteroids)
3. Results in significant hyperglycemia, dehydration, and ketoacidosis
4. Common signs and symptoms: Polyuria, polydipsia, vomiting, dehydration, weakness, altered mental status, coma, abdominal pain, Kussmaul respirations, tachycardia, hyponatremia, hyperkalemia
5. Treatment
    a. Treat underlying cause, if known.
    b. Fluid replacement
        i. 0.45%–0.9% sodium chloride, depending on baseline serum sodium concentrations
        ii. Change to 5% dextrose with 0.45% sodium chloride when serum glucose is less than 200 mg/dL.
    c. Insulin
        i. Goal is to stop ketosis, not to normalize glucose concentrations.
        ii. Intravenous bolus regular insulin: 0.1 unit/kg
        iii. Intravenous infusion
            (a) 0.1 unit/kg/hour regular insulin (increase if not a 50- to 75-mg/dL decrease in serum glucose in the first hour)
            (b) Alternatively, 0.14 unit/kg/hour if no insulin bolus is given
            (c) If not at least a 10% decrease in serum glucose attained in first hour, give 0.14-unit/kg intravenous bolus
            (d) Reduce infusion rate to 0.02–0.05 unit/kg/hour when serum glucose reaches 200 mg/dL, and keep glucose of 150–200 mg/dL until DKA resolves.
        iv. Interrupt insulin treatment if baseline serum potassium is less than 3.3 mEq/L and until corrected.
    d. Potassium
        i. Potassium 20–30 mEq/L of intravenous fluid if baseline serum potassium greater than 3.3 but less than 5.3 mEq/L
        ii. Hold if 5.3 mEq/L or greater initially. Monitor and replace as needed.
        iii. Potassium 20–30 mEq/hour if baseline less than 3.3 mEq/L
    e. Intravenous bicarbonate if serum pH less than 6.9
    f. DKA considered resolved and can be converted to subcutaneous insulin when serum glucose is less than 200 mg/dL and at least two of the following:
        i. Venous pH greater than 7.3
        ii. Serum bicarbonate of 15 mEq/L or greater
        iii. Calculated anion gap of 12 mEq/L or less

C. Nephropathy
   1. Screen annually with random spot collection of urine albumin/creatinine ratio, starting at diagnosis in T2D and after 5 or more years in T1D.
      a. Normal: Less than 30 mg/g (or micrograms per milligram)
      b. Increased urinary albumin excretion (albuminuria) 30 mg/g or greater
      c. Two of three specimens greater than 30 mg/g obtained over 3–6 months is consistent with a diagnosis of albuminuria
      d. The ADA no longer uses the terms *microalbuminuria* and *macroalbuminuria*.
   2. Estimated CrCl yearly
   3. ACE inhibitors or ARBs are considered the initial treatment of choice if urine albumin/creatinine concentrations are greater than 30 mg/g.
   4. Dietary protein restriction as renal function declines
   5. Canagliflozin in patients with decreased renal function and significantly elevated albuminuria is FDA approved to reduce decline in eGFR and reduce risk of developing end-stage renal disease.

D. Retinopathy
   1. Screen annually with dilated and comprehensive eye examinations, starting at diagnosis in T2D and after 5 or more years in T1D.
   2. Frequency can be reduced to every 2–3 years after one or more normal examinations.
   3. Appropriately control glucose concentrations, cholesterol, and blood pressure.
   4. Severe forms of retinopathy (e.g., proliferative retinopathy, macular edema) can be treated with intravitreous steroids or antivascular endothelial growth factor with or without photocoagulation.

E. DM Neuropathies
   1. Can have nerve damage in any area of the body, but commonly affects the lower extremities
   2. Screen for distal polyneuropathy
      a. Screen after 5 years in T1D and at diagnosis in T2D, then yearly thereafter
      b. Diminished sensitivity is a significant risk factor for diabetes-related foot ulcers and increases the need for frequent visual inspection by patients, if it exists.
   3. Symptoms are patient-specific but can include numbness, burning, tingling sensation, or pain.
   4. Treatment of neuropathies should focus on glycemic control to minimize disease progression. Therapies for symptomatic improvement do not prevent progression.
   5. Neuropathic pain therapy
      a. ADA recommendations consider duloxetine, gabapentin, or pregabalin as initial therapy.
      b. Tricyclic antidepressants (amitriptyline, desipramine)
         i. Effective but limited because of anticholinergic effects; some recommend using secondary amine tricyclic antidepressants (e.g., desipramine, nortriptyline) because they may have less anticholinergic effect than tertiary amines (e.g., amitriptyline, imipramine)
         ii. Daily dose is less than doses used for depression.
      c. Anticonvulsants (gabapentin, lamotrigine, pregabalin)
         i. Comparative data on gabapentin and pregabalin against tricyclic antidepressants show similar efficacy with fewer adverse effects. Adverse effect profile is still significant (e.g., fatigue, dizziness).
         ii. Pregabalin is the only anticonvulsant approved for use in DM neuropathic pain.

d. Selective serotonin reuptake inhibitor/selective serotonin and norepinephrine reuptake inhibitor (duloxetine, paroxetine, citalopram)
    i. Duloxetine is the only approved agent in this category.
    ii. Duloxetine data compared with amitriptyline data show similar efficacy and expected higher anticholinergic adverse effects with amitriptyline.
    iii. Duloxetine may provide better pain reduction, with tolerability similar to that of pregabalin.
e. Tramadol/acetaminophen: As effective as gabapentin; different adverse effect profile
f. Opioids: Tapentadol extended release is the only approved agent in this class; no head-to-head efficacy studies

6. Gastroparesis therapy
    a. Autonomic neuropathy causes nausea and vomiting after meals because of delayed gastric emptying.
    b. Nonpharmacologic strategies
        i. More frequent but smaller meals
        ii. Homogenize food
        iii. Decrease fat and fiber in diet
        iv. Gastric pacemaker
    c. Pharmacologic treatment
        i. Metoclopramide: 10 mg orally or 15 mg intranasally before meals; risk of tardive dyskinesia or extrapyramidal reactions, chronic use should assess the benefit-risk of continued therapy
        ii. Erythromycin: 40–250 mg before meals for up to 1 month

F. Cardiovascular Disease
1. Most common cause of morbidity and mortality and health care expenditures in DM complications
2. Proper DM management should always focus on cardiovascular disease risk reduction (review cardiovascular chapters).
3. Stress and continually assess the blood pressure and lipid goals described earlier.
4. Blood pressure management
    a. Often requires more antihypertensive medications
    b. Hypertensive regimen should include an ACE inhibitor, ARB, dihydropyridine calcium channel blocker, or thiazide-like diuretic.
    c. If both hypertension and increased urine albumin excretion are present, first-line therapy is an ACE inhibitor or an ARB.
    d. Administration of at least one antihypertensive in the evening may improve blood pressure and reduce cardiovascular outcomes.
5. Lipid management (according to the ADA)
    a. Assess fasting lipid profile annually or as needed to monitor adherence.
    b. Statin therapy recommendations are based on age and cardiovascular risk.
        i. Moderate-dose statin therapy is recommended for all patients age 40–75 without cardiovascular risk factors (e.g., LDL of 100 mg/dL or greater, high blood pressure, smoker, overweight or obese).
        ii. High-dose statin therapy should be considered for those with multiple cardiovascular risk factors.
        iii. High-dose statin therapy is recommended for all patients with existing cardiovascular disease (e.g., previous cardiovascular event or acute coronary syndrome) or a 10-year cardiovascular disease risk greater than 20%.
        iv. For patients with atherosclerotic cardiovascular disease and LDL greater than 70 mg/dL despite statin therapy, consider additional LDL-lowering therapy.
        v. Statin doses are consistent with the ACC/AHA lipid guidelines.

6. Antiplatelet therapy
    a. Low-dose aspirin (75–162 mg/day)
        i. With existing cardiovascular disease
        ii. Consider as part of primary prevention if at an increased cardiovascular risk
    b. Clopidogrel for those intolerant of aspirin therapy

G. Preventive Immunizations
1. Annual influenza vaccine
2. Pneumococcal polysaccharide vaccine
3. Hepatitis B vaccine

VIII. OTHER DIABETES MEDICATION ISSUES

A. Former FDA Risk Evaluation and Mitigation Strategy for Rosiglitazone (removed November 2013)
1. The strategy limited the use and distribution of rosiglitazone because of concerns for increased myocardial events.
2. Subsequent review of clinical trial data suggests no increased risk of myocardial infarction, resulting in removal of strategy.
3. Despite the removal of the strategy, rosiglitazone remains unavailable.

B. In the wake of the rosiglitazone safety issue, the FDA required all newly approved diabetes medications to prove cardiovascular safety between 2008 and 2020.
1. At least 2 years of safety data that include cardiovascular events as an end point and independent adjudication of events
2. Necessary to study in older adults and in those with some degree of renal impairment and those with more advanced diabetes
3. No study showed a significant increase in cardiovascular risk.
4. In March 2020, the FDA drafted new guidance on this issue and no longer recommends that drug manufacturers conduct cardiovascular safety studies.

IX. DIABETES INSIPIDUS

A. Diabetes insipidus (DI) is usually a result of decreased production of antidiuretic hormone, also known as *vasopressin*, in central DI, or a lack of antidiuretic hormone effect in the kidneys (nephrogenic DI).

B. Classification
1. Central or neurogenic
    a. Idiopathic
    b. Trauma (brain injury)
    c. Neoplasm
    d. Hypodipsia
    e. Genetic abnormality

2. Nephrogenic
    a. Genetic abnormality
    b. Acquired (more common)
        i. Drug induced (e.g., lithium, amphotericin B, foscarnet, cidofovir)
        ii. Kidney disease (e.g., polycystic kidney disease, obstruction)
        iii. Electrolyte disorder (hypercalcemia, hypokalemia)

C. Diagnosis
1. Elevated urine volume (greater than 3 L/day)
2. Decreased urine osmolarity (less than 200 mOsm/kg)
3. Response to water deprivation (may help differentiate between nephrogenic and central etiology in non–critically ill patients)

D. Signs and Symptoms
1. Polydipsia
2. Polyuria or nocturia
3. Weakness or lethargy
4. Confusion or delirium (if severe)

E. Treatment
1. Treat underlying cause, if known.
2. Central DI
    a. Desmopressin: 5–20 mcg intranasally once or twice daily
    b. Adjunctive therapies: Chlorpropamide, carbamazepine
3. Nephrogenic DI
    a. Thiazide diuretic
    b. Dietary sodium restriction
    c. Indomethacin

REFERENCES

Thyroid Disorders

1. Alexander E, Pearce E, Brent G, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315-89.
2. Garber J, Cobin R, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 2012;22:1200-35.
3. Jonklaas J, Bianco A, Bauer A, et al. Guidelines for the treatment of hypothyroidism prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid 2014;24:1670-1751.
4. Kane MP, Bakst G. Thyroid disorders. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020. Available at https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=223397495. Accessed November 17, 2020.
5. Rahn R, Burch H, Cooper D, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract 2011;17:e1-65.
6. Ross D, Burch H, Cooper D, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-437.
7. Smith T, Hegedus L. Graves' disease. N Engl J Med 2016;375:1552-65.

Pituitary Gland Disorders

1. Jordan JK, Sheehan A, Munir K. Pituitary gland disorders. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020. Available at https://accesspharmacy-mhmedical-com.ezproxy.ttuhsc.edu/content.aspx?Accebookid=2577&sectionid=219311270. Accessed July 21, 2020.
2. Melmed S, Casanueva F, Hoffman A, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:273-88.
3. Molitch M. Diagnosis and treatment of pituitary adenomas: a review. JAMA 2017;317:516-24.
4. Thorogood N, Baldeweg S. Pituitary disorders: an overview for the general physician. Br J Hosp Med 2008;69:198-204.

Adrenal Gland Disorders

1. Biller B, Grossman A, Stewart P, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 2008;93:2454-62.
2. Shalet S, Mukherjee A. Pharmacological treatment of hypercortisolism. Curr Opin Endocrinol Diabetes Obes 2008;15:234-8.
3. Smith SM, Garland SG, Gums JG. Adrenal gland disorders. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020. Available at https://accesspharmacy-mhmedical-com.ezproxy.ttuhsc.edu/content.aspx?bookid=2577&sectionid=221104771. Accessed July 21, 2020.
4. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:2807-31.

Obesity

1. Apovian C, Aronne L, Bessesen D, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342-62.
2. Garvey W, Mechanick J, Brett E, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016;22 (suppl 3):1-203.
3. Jensen M, Ryan D, Apovian C, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American

College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. J Am Coll Cardiol 2014;63:2985-3023.

Polycystic Ovary Syndrome

1. Legro R, Arslanian S, Ehrmann D, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4565-92.
2. McCartney C, Marshall R. Polycystic ovary syndrome. N Engl J Med 2016;375:54-64.
3. Nestler J. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med 2008; 358:47-54.
4. Polycystic ovary syndrome. ACOG Practice Bulletin No. 194. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e157-71.

Diabetes Mellitus and Insipidus

1. American Diabetes Association (ADA). Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. Diabetes Care 2020;43(suppl 1):S14-31.
2. American Diabetes Association (ADA). Management care in the hospital: standards of medical care in diabetes-2020. Diabetes Care 2020;43(suppl 1):S193-202.
3. American Diabetes Association (ADA). Glycemic targets: standards of medical care in diabetes-2020. Diabetes Care 2020;43(suppl 1):S66-76.
4. American Diabetes Association (ADA). Pharmacological approaches to glycemic treatment: standards of medical care in diabetes-2020. Diabetes Care 2020;43(suppl 1):S98-110.
5. American Diabetes Association (ADA). Cardiovascular disease and risk management: standards of medical care in diabetes-2020. Diabetes Care 2020;43(suppl 1):S111-134.
6. American Diabetes Association (ADA). Microvascular complications and foot care: standards of medical care in diabetes-2020. Diabetes Care 2020;43(suppl 1):S135-151.
7. Blevins L, Wand G. Diabetes insipidus. Crit Care Med 1992;20:69-79.
8. Chessman KH, Haney J. Disorders of sodium and water homeostasis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill, 2017:chap 49. Available at http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146061710. Accessed November 29, 2017.
9. Davies M, D'Alessio D, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.
10. Garber A, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2020 executive summary. Endocr Pract 2020;26:107-39..
11. Kitabchi A, Umpierrez G, Miles J, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335-43.
12. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA. Guidelines on the management of blood cholesterol in diabetes. Diabetes Care 2020;43:1673-8.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D
Given this patient's reluctance to undergo ablative therapy, oral therapy is warranted. Methimazole (Answer D) is recommended over propylthiouracil (Answer B) because it is associated with a lower risk of hepatotoxicity, though it may not be more efficacious. Answer A is incorrect because iodine therapy is indicated in this type of case only before surgery or during an acute case of thyroid storm. Answer C is incorrect; although β-blockers might provide some symptomatic relief, they would do little to stabilize this patient's thyroid concentrations.

2. Answer: A
This patient has hypothyroidism, given her elevated TSH and low free T_4, caused by Hashimoto disease. Levothyroxine (Answer A) is the drug of choice for this condition, given its adverse effect profile, cost, antigenicity profile, and uniform potency. Although liothyronine can be used for hypothyroidism, its potential for increasing the risk of cardiovascular complications makes it second line (Answer B). Answer C is also incorrect, given its increased antigenicity compared with levothyroxine. Answer D is incorrect because it is used to treat hyperthyroidism.

3. Answer: D
Fluoxetine (Answer D), a selective serotonin reuptake inhibitor, can cause drug-induced hyperprolactinemia. Answer A is incorrect because calcium channel blockers are not associated with an elevated risk of this condition. Given the patient's normal pituitary and thyroid tests, Answer B, prolactin-secreting adenoma, is probably incorrect. Answer C is incorrect because pregnancy is not associated with an elevated risk of this condition.

4. Answer: D
Because the patient's aldosterone/renin ratio and blood pressure are high, hyperaldosteronism (Answer D) is the most likely disease listed. Cushing syndrome and hyperaldosteronism can be secondary causes of hypertension. In this case, the patient's free 24-hour urine cortisol is normal but would be elevated if he had Cushing syndrome, making Answer A incorrect. Answer B is incorrect because Addison disease is a result of cortisol deficiency and is not associated with hypertension. Answer C, hyperprolactinemia, is unlikely, given the patient's presentation and his abnormal aldosterone/renin ratio.

5. Answer: B
The minimal weight loss after 12 weeks of therapy with phentermine/topiramate should be 5%; otherwise, the medication should be discontinued. Given this patient's baseline weight, at least 5.9 kg (13 lb), Answer B, is necessary to continue therapy. The other answers provided are too low (Answer A) or exceed the 5% minimal expectation (Answers C and D).

6. Answer: D
Historically, the ADA has recommended a subsequent test of hyperglycemia to be performed at another date. Update recommendations state that two different tests of hyperglycemia can be obtained on the same day and sample. In this case, Answer D is correct; an A1C in addition to the obtained glucose concentration can be obtained. Answers A and B would only be correct if the patient had signs or symptoms of hyperglycemia. Answer C is not recommended because the concentration has already been obtained.

7. Answer: B
Improved blood pressure control has been associated with a decrease in both microvascular (e.g., nephropathy) and macrovascular (e.g., myocardial infarction) complications. Answer B is the only option that directly affects blood pressure. Answers A and C address only hyperglycemia, which may improve microvascular complications but not macrovascular complications. Answer D, niacin, has not been shown to reduce either complication in patients with diabetes.

8. Answer: C
This patient's TDI requirement is 40 units (80 kg × 0.5 unit/kg/day). Half of this is initially used for basal insulin requirements and half for bolus insulin requirements before meals. The 20 units for bolus requirements should initially be divided equally between three meals (i.e., 6–7 units), making Answer C correct. The other three answers would provide either too much (Answer D is incorrect) or too little (Answers A and B are incorrect) estimated insulin at each meal.

9. Answer: B

The GLP-1 agonists mildly reduce weight when used to treat hyperglycemia in patients with T2D. Answer B, liraglutide, is the only GLP-1 provided. Each of the other options, a sulfonylurea (Answer A), a thiazolidinedione (Answer C), and insulin (Answer D), is associated with weight gain.

10. Answer: D

The usual next step in therapy for a patient no longer able to maintain adequate glycemic control with monotherapy is to add agents. Answer D adds to the existing metformin therapy and provides for a sufficient A1C reduction. Answer A is incorrect because the patient is already exercising and still has uncontrolled hyperglycemia. Answer B is incorrect because one agent, particularly metformin, would not normally be changed to another unless a patient were having adverse effects from the original agent. Answer C, bromocriptine, would probably not provide sufficient glycemic control, given this patient's current A1C.

11. Answer: A

In this case, initiation of medications for a patient with newly diagnosed hyperglycemia is complicated by the patient's many comorbidities. Normally, metformin, Answer D, would be the initial treatment of choice, but the patient's renal function is poor, and metformin should not be used. Answer C, exenatide, is also incorrect because it, too, should not be used in patients with significant renal impairment. Given the patient's existing edema and history of heart failure, pioglitazone (Answer B) is contraindicated because it can aggravate the conditions. Answer A, linagliptin, is the most appropriate choice because the patient's A1C is not markedly elevated, and renal function does not need to be considered.

12. Answer: A

Current recommendations call for an ACE inhibitor or an ARB if a patient has elevated urinary albumin excretion. This patient's blood pressure is at goal (less than 140/90 mm Hg), and urine albumin/creatinine is normal (less than 30 mg/g), making Answer A correct. No additional therapy is necessary. Answers B and C are incorrect because the patient's blood pressure is well controlled and urine albumin/creatinine is normal. Answer D is incorrect because protein restriction is used only after a significant decrease in CrCl, and this patient has normal renal function.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D
According to the ADA guidelines, patients with this degree of hyperglycemia should be initiated on insulin therapy, and Answer D provides an appropriate basal and bolus insulin combination. This patient's A1C is greater than 10%, and his fasting glucose is greater than 300–350 mg/dL. Answers A and C are not optimal because dual therapy with oral agents would probably not bring this patient to his glycemic goal. Answer B is also not optimal because the combination of a sulfonylurea and rapid-acting insulin would increase the risk of hypoglycemia and would probably not sufficiently reduce the A1C.

2. Answer: A
The weight-based initial estimate of total basal insulin needs is 50% of the calculated TDI. The TDI for this patient is 26 units (0.4 unit/kg/day × 65 kg). Half of that is 13 units. Answer C is incorrect; although insulin glargine is a basal insulin, the calculated dose would provide too much insulin and would likely cause significant hypoglycemia. Answers B and D are incorrect because they both use a type of insulin reserved for bolus and correctional insulin dosing. Answer A is correct because the estimated dose and type of insulin are appropriate.

3. Answer: C
This patient has an elevated blood pressure, poor renal function, and two urine albumin/creatinine concentrations above 30 mg/g. According to the ADA and the clinical literature, the best classes of medications for patients with this condition are ARBs and ACE inhibitors, making Answer C correct. Answer A (thiazide diuretic) is inappropriate because this class of medications is not as beneficial as agents that block the renin-angiotensin system. Answer B, a dihydropyridine calcium channel blocker, is incorrect for the same reason. Answer D, a non-dihydropyridine calcium channel blocker, is an alternative to agents that block the renin-angiotensin system but should not be used instead of these agents unless a patient has a contraindication.

4. Answer: B
Unlike methimazole, propylthiouracil (Answer B) has a boxed warning about the risk of hepatotoxicity. Answer A is incorrect because neither agent is considered more efficacious than the other. Answer C is incorrect because Hashimoto disease is a result of hypothyroidism, not hyperthyroidism. Methimazole is dosed once daily, whereas propylthiouracil is usually dosed up to three times daily, making Answer D incorrect.

5. Answer: A
Ketoconazole (Answer A) is used in patients with Cushing syndrome because it reduces cortisol synthesis. Answer B, spironolactone, is used in patients with hyperaldosteronism. Answer C is inappropriate because Cushing syndrome results in cortisol concentrations that are too high, and adding a corticosteroid to treat its symptoms could make the problem worse. Bromocriptine, Answer D, is used to treat acromegaly, not Cushing syndrome.

6. Answer: C
This patient has both significant renal impairment and a markedly elevated A1C. Answers A and D are incorrect because they are both contraindicated in patients with significant renal impairment. Answer B is also incorrect. Although alogliptin can be used in patients with renal impairment at a reduced dosage, it would probably not sufficiently reduce the A1C. Initiating insulin is the best option in this case because insulin can be used in patients with renal impairment and can be titrated to attain significant reductions in A1C (Answer C is correct).

7. Answer: A
An older woman with heart disease should be initiated on a lower initial dose (Answer A) of levothyroxine. Answer B is the normal starting dose (i.e., 1.6 mcg/kg) but is probably too high an initial dose for an older adult with established heart disease. Answers C and D are incorrect because the drug of choice is levothyroxine, and liothyronine is no longer recommended for this condition.

8. Answer: B
For insulin adjustments, determine which BG readings are at goal and which are not. For BG readings consistently not at goal, determine which insulin is most affecting the readings. In this case, the patient's BG readings are consistently elevated at bedtime, which is probably caused by insufficient predinner prandial (i.e.,

bolus) insulin. Increasing the predinner rapid-acting insulin, Answer B, should effectively lower the bedtime concentrations. Changing the rapid-acting insulin at other times of the day would not help, making Answers A and D incorrect. Changing the patient's basal insulin (glargine) would probably not help her bedtime BG and, because her FBG readings have been well controlled, could lead to hypoglycemia (Answer C).

9. Answer: A

This patient has mild symptoms, and her ablative therapy worked initially but now no longer controls her thyroid concentrations. Methimazole (Answer A) would be the preferred oral agent, given its dosing frequency and lower risk of hepatotoxicity compared with propylthiouracil (Answer C). Lugol's solution is used only temporarily and not chronically, making Answer B incorrect. Answer D is not optimal; β-blockers, which may provide symptomatic relief, would not significantly affect her thyroid concentrations.

10. Answer: D

This patient has good control of his fasting glucose but has postprandial hyperglycemia. An agent that targets postprandial glucose (e.g., a DPP-4 inhibitor, Answer D) would be most appropriate. Answer A is incorrect because this would exceed the maximal daily dose for metformin. Answer B is incorrect; although insulin glargine is a basal insulin that affects FPG, it has little effect on postprandial glucose. Answer C is incorrect, again because it is a basal insulin and because it is more appropriate to add medications than to change to another agent unless the patient is experiencing adverse effects with the first agent.

11. Answer: D

This patient has tried dieting and exercise, but these have failed to control her weight; thus, her current routine alone is inappropriate, making Answer A incorrect. Answer B, liraglutide, is approved for the treatment of obesity at high doses. However, this patient's A1C is at goal, and she is experiencing some bouts of low blood glucose; thus, the initial dose is too high, making this answer incorrect. Answer C is a federally scheduled medication because of its abuse potential with phentermine and, given this patient's history of substance abuse, would not be the most favorable selection, though it is not specifically contraindicated in this patient. Orlistat, Answer D, is the only agent listed to which this patient does not have a specific precaution or contraindication for its use.

12. Answer: A

This patient has now had two laboratory glycemic indicators (A1C and FBG) consistent with the diagnosis of diabetes, making Answer A correct. Answer B is probably incorrect because this patient has several risk factors for developing T2D, including obesity, ethnicity, age, a history of gestational diabetes, and a strong family history of the disease. Answer C is incorrect because there is no need to obtain another A1C reading this soon after the reading just 2 weeks ago, and the A1C can be used in the diagnosis of diabetes. Obtaining another glucose reading on another day (Answer D) is also incorrect, again because there are already two abnormal glycemic indicators; therefore, another is not necessary to confirm the diagnosis.

13. Answer: C

According to the ADA, moderate-dose statin therapy (Answer C) is recommended for patients older than 40 with diabetes but without established cardiovascular disease. In this case, the patient's glycemic and blood pressure readings are at goal (less than 7.0% and less than 140/90 mm Hg, respectively). Adding insulin (Answer A) and adding a blood pressure medication (Answer B) would not be necessary. Answer D is incorrect because this patient does not need fibrate therapy; his HDL and TG are under control.

Oncology Supportive Care

Christopher T. Elder, Pharm.D., BCOP

Lloyd L. Gregory School of Pharmacy
Palm Beach Atlantic University
West Palm Beach, Florida

Oncology Supportive Care

Christopher T. Elder, Pharm.D., BCOP

Lloyd L. Gregory School of Pharmacy
Palm Beach Atlantic University
West Palm Beach, Florida

Learning Objectives

1. Identify, assess, and recommend appropriate pharmacotherapy for managing common complications of cancer chemotherapy, including nausea and vomiting, myelosuppression and the appropriate use of growth factors, infection, anemia and fatigue, cardiotoxicity, and extravasation injury.
2. Assess and recommend appropriate pharmacotherapy for managing cancer-related pain.
3. Assess and recommend appropriate pharmacotherapy for managing oncologic emergencies, including hypercalcemia, tumor lysis syndrome, and spinal cord compression.

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 50-year-old man is in the clinic to receive his third cycle of R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisone, and rituximab) for non-Hodgkin lymphoma. He is very anxious, with nausea and vomiting lasting for about 12 hours after his previous cycle of chemotherapy. The antiemetic regimen he received for his previous cycle of chemotherapy was granisetron 1 dose plus dexamethasone 1 dose administered 30 minutes before chemotherapy. Which regimen is most appropriate for the patient to receive on day 1 of the next cycle of chemotherapy?
   A. Granisetron 1 dose plus dexamethasone 1 dose administered 30 minutes before chemotherapy.
   B. Dolasetron 1 dose plus dexamethasone 1 dose plus aprepitant 1 dose administered 30 minutes before chemotherapy.
   C. Netupitant/palonosetron 1 dose plus dexamethasone 1 dose plus lorazepam 1 dose administered 30 minutes before chemotherapy.
   D. Metoclopramide 1 dose plus dexamethasone 1 dose plus aprepitant 1 dose administered 30 minutes before chemotherapy.

2. A 65-year-old man with metastatic non–small cell lung cancer is brought to the clinic by his family because he is lethargic and fatigued. Pertinent laboratory values include serum calcium concentration 12 mg/dL and albumin concentration 2 g/dL. Which therapy is best for this patient's lethargy and fatigue as the result of hypercalcemia of malignancy?
   A. Calcitonin 4 units/kg every 12 hours.
   B. Furosemide 20 mg orally.
   C. Dexamethasone 10 mg orally two times a day.
   D. Zoledronic acid 4 mg intravenously.

3. A 20-year-old man was recently given a diagnosis of acute myeloid leukemia. He has an elevated white blood cell count (WBC), and he will receive chemotherapy tomorrow. Which is the best prevention strategy for tumor lysis syndrome (TLS)?
   A. Hydration with 5% dextrose (D_5W), 1 L before chemotherapy, plus allopurinol 300 mg/day.
   B. Hydration with D_5W, 100 mL/hour starting at least 24 hours before chemotherapy, plus allopurinol 300 mg/day.
   C. Hydration with normal saline 250 mL/hour starting at least 24 hours before chemotherapy plus allopurinol 300 mg/day.
   D. Hydration with normal saline 100 mL/hour starting at least 24 hours before chemotherapy plus sodium bicarbonate 500 mg orally every 6 hours.

4. An 18-year-old man is about to begin chemotherapy with curative intent for acute lymphoblastic leukemia. On today's complete blood cell count (CBC), his hemoglobin (Hgb) is 7 g/dL, and he is experiencing fatigue. Which is the best treatment recommendation?
   A. Initiate epoetin.
   B. Administer transfusion of packed red blood cells (RBCs).
   C. Delay chemotherapy treatment until Hgb recovers.
   D. Reduce chemotherapy dosages to prevent further decreases in Hgb.

Questions 5–7 pertain to the following case.
A patient received her fourth cycle of chemotherapy with paclitaxel/carboplatin for ovarian cancer 12 days ago. She reports to the clinic this morning with a temperature of 103°F. Her CBC is WBC 500 cells/mm^3, segmented neutrophils 55%, band neutrophils 5%, basophils 15%, eosinophils 5%, monocytes 15%, and platelet count 99,000 cells/mm^3. She denies any signs or symptoms of infection. Her blood pressure is 115/60 mm Hg, heart rate is 80 beats/minute, and respiratory rate is 15 breaths/minute.

5. Which best represents the patient's absolute neutrophil count (ANC)?
   A. 275 cells/mm^3.
   B. 300 cells/mm^3.
   C. 25 cells/mm^3.
   D. 500 cells/mm^3.

6. Which is the best course of action for this patient?
   A. Admit her to the hospital for parenteral antibiotic drugs.
   B. Treat her as an outpatient with antibiotic drugs.
   C. Initiate a colony-stimulating factor (CSF).
   D. Discontinue chemotherapy.

7. Which statement about this patient is most accurate?
   A. Given her monocyte count, her neutropenia is expected to last for another week.
   B. This is a nadir neutrophil count, and neutrophils would be expected to start increasing soon.
   C. The elevated absolute eosinophil count indicates an allergic reaction to carboplatin.
   D. It is unusual for the ANC to be this low in the setting of an elevated platelet count.

8. A 60-year-old man has head and neck cancer with extensive involvement of facial nerves. His pain medications include transdermal fentanyl 100 mcg/hour every 72 hours and oral morphine solution 40 mg every 4 hours as needed. He is still having problems with neuropathic pain. Which treatment is best to recommend?
   A. Begin gabapentin and decrease the dosage of fentanyl.
   B. Increase the dosages of fentanyl and morphine.
   C. Begin diazepam and increase the dosage of fentanyl.
   D. Begin gabapentin and continue fentanyl and morphine at the same dosage.

9. A patient is receiving chemotherapy for limited-stage small cell lung carcinoma. After the third cycle of chemotherapy, she is hospitalized with febrile neutropenia. She recovers, and today she is scheduled to receive the fourth cycle of chemotherapy. Which statement is the best treatment course for this patient?
   A. The patient should receive filgrastim 250 mcg/m^2/day subcutaneously for 10 days, given at least 24 hours after chemotherapy.
   B. The patient should receive filgrastim 5 mcg/kg/day subcutaneously, starting today.
   C. The patient should receive pegfilgrastim 1 mg/day subcutaneously for 6 days, given at least 24 hours after chemotherapy.
   D. The patient should receive filgrastim 5 mcg/kg/day subcutaneously for 7 days, given at least 24 hours after chemotherapy.

10. A 60-year-old woman with breast cancer is to begin chemotherapy with AC (doxorubicin and cyclophosphamide). Laboratory values today include sodium 140 mEq/L, potassium 3.8 mEq/L, glucose 100 mg/dL, serum creatinine 1.1 mg/dL, aspartate aminotransferase 6 IU/L, alanine aminotransferase 35 IU/L, and total bilirubin 2 mg/dL. Which statement is most appropriate?
    A. The dosage of doxorubicin should be decreased.
    B. The dosage of cyclophosphamide should be decreased.
    C. Both chemotherapy drugs should be given at standard dosages.
    D. Both chemotherapy drugs should be given at decreased dosages.

11. Large cell lymphoma is considered intermediate (between indolent and highly aggressive) in tumor growth and biology. Large cell lymphoma is sensitive to chemotherapy and potentially curable. Metastatic colorectal cancer is considered slow growing. Although responses to chemotherapy commonly occur and chemotherapy can prolong survival (by months), metastatic colorectal cancer is not generally considered curable with chemotherapy. Given these differences between large cell lymphoma and metastatic colorectal cancer, which statement is most accurate?
    A. Patients with large cell lymphoma should receive allopurinol before the first cycle of chemotherapy because they are at an elevated risk of developing TLS.
    B. Patients with metastatic colorectal cancer should receive allopurinol before the first cycle of chemotherapy because they are at an elevated risk of developing TLS.
    C. Patients with large cell lymphoma should receive pamidronate before the first cycle of chemotherapy because they are at an elevated risk of developing hypercalcemia.
    D. Patients with metastatic colorectal cancer should receive pamidronate before the first cycle of chemotherapy because they are at an elevated risk of developing hypercalcemia.

Questions 12 and 13 pertain to the following case.

12. Consider the information provided earlier about large cell lymphoma and metastatic colorectal cancer. Patient 1 with large cell lymphoma is receiving R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisone, and rituximab) chemotherapy. Patient 2 with metastatic colorectal cancer is receiving FOLFIRI (fluorouracil-leucovorin, irinotecan) chemotherapy. On the day cycle 2 is due, both patients have an ANC of 800 cells/mm^3. Which statement is most appropriate, given the ANC values?
    A. Patient 1 should receive chemotherapy to keep him on schedule because he has a curable disease.
    B. Patient 2 should receive chemotherapy to keep him on schedule because he has a curable disease.
    C. The chemotherapy for patient 1 should be held for now, and he should receive filgrastim after the next time he has chemotherapy.
    D. The chemotherapy for patient 2 should be held for now, and he should receive filgrastim after the next time he has chemotherapy.

13. Sometimes, extravasation is not immediately evident when it occurs. Immediately after patient 1 receives R-CHOP, an extravasation is suspected. Which is the best treatment recommendation for the patient's extravasation?
    A. Application of a warm pack for suspected extravasation of doxorubicin.
    B. Application of a cold pack for suspected extravasation of vincristine.
    C. Parenteral dexrazoxane for suspected extravasation of doxorubicin.
    D. Application of sodium thiosulfate for suspected extravasation of vincristine.

14. A 65-year-old man with metastatic melanoma is being treated with nivolumab and ipilimumab. After treatment cycle 3, he presents to the emergency department with concerns of fatigue and uncontrolled diarrhea. He reports 8 loose stools per day for the past 4 days. On examination, the patient appears dehydrated. Which is the best course of management at this time?
    A. Initiate intravenous fluid replacement and intravenous methylprednisolone 2 mg/kg/day. Patient will need inpatient admission and monitoring until improvement.
    B. Initiate intravenous fluid replacement with 1 L of normal saline. Discharge patient on loperamide 4 mg by mouth once, followed by 2 mg after each loose stool until symptoms improve.
    C. Initiate intravenous fluid replacement with 1 L of normal saline. Discharge patient and discontinue immunotherapy.
    D. Initiate intravenous fluid replacement with 1 L of normal saline. Discharge patient with a prescription for a prednisone taper of 20 mg once daily for 3 days, followed by 15 mg once daily for 3 days, then 10 mg once daily for 3 days, then 5 mg once daily for 3 days, then 2.5 mg for 3 days; then discontinue.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Tasks 1, 4
    b. Systems and Patient-Care Problems:
        i. Antiemetics
        ii. Pain Management
        iii. Treatment of Febrile Neutropenia
        iv. Use of CSFs in Neutropenia and Febrile Neutropenia
        v. Thrombocytopenia
        vi. Anemia/Fatigue
        vii. Chemoprotectants
        viii. Oncology Emergencies
        ix. Miscellaneous Antineoplastic Pharmacotherapy
2. Domain 3: System-Based Standards and Population-Based Pharmacotherapy
    a. Tasks 1, 3, 6

I. ANTIEMETICS

A. Important Definitions Pertaining to Chemotherapy-Induced Nausea and Vomiting (CINV)
   1. Nausea is described as an awareness of discomfort that may or may not precede vomiting; nausea is accompanied by decreased gastric tone and decreased peristalsis.
   2. Retching is the labored movement of abdominal and thoracic muscles associated with vomiting without the expulsion of vomitus (also called dry heaves).
   3. Vomiting (emesis) is the ejection or expulsion of gastric contents through the mouth.
      a. Acute onset: Occurs 0–24 hours after chemotherapy administration and commonly resolves within 24 hours (intensity peaks after 5–6 hours)
      b. Delayed onset: Occurs more than 24 hours after chemotherapy administration
         i. Delayed symptoms are best described with cisplatin, although they are commonly reported in association with other agents (carboplatin or doxorubicin).
         ii. The distinction between acute and delayed symptoms with respect to time of onset is somewhat arbitrary, and it becomes blurred when chemotherapy is administered for several consecutive days.
         iii. The importance of the distinction between acute and delayed (and anticipatory) symptoms is that they likely have different mechanisms and therefore different management strategies.
   4. Anticipatory vomiting (or nausea) is triggered by sights, smells, or sounds and is a conditioned response; it is more likely to occur in patients whose previous post-chemotherapy nausea and vomiting was not well controlled.
   5. Breakthrough emesis occurs despite prophylactic treatment or necessitates additional rescue medications.
   6. Refractory emesis is emesis that occurs during treatment cycles when antiemetic prophylaxis or rescue therapy has failed in previous cycles.

B. Risk Factors for CINV
   1. Patient-related risk factors
      a. Younger age (younger than 50)
      b. Female sex
      c. History of motion sickness
      d. History of nausea or vomiting during pregnancy
      e. Poor control of nausea or vomiting in previous chemotherapy cycles
      f. Little or no previous alcohol use
      g. Anxiety/high pretreatment expectation of nausea
   2. Emetogenicity of chemotherapy agents: Several schemes for assessing emetogenicity have been proposed.
      a. Originally, emetogenic risk was classified as "none," "mild," "moderate," or "severe."
      b. The Hesketh model, proposed in 1997, classified emetogenic risk as levels ranging from level 1 (less than 10% frequency of emesis) to 5 (more than 90% frequency of emesis).
      c. Current model includes four levels for parenteral chemotherapy and two levels for oral chemotherapy.
      d. Levels for parenteral chemotherapy (e.g., minimal, low, moderate, high emetogenic risk) are defined by the percentage of patients expected to experience emesis when not receiving antiemetic prophylaxis. (See Table 1)
      e. Levels for oral chemotherapy (prophylaxis recommended or as needed)

3. Radiation therapy can also cause nausea and vomiting. The incidence and severity of radiation-induced nausea and vomiting vary by site of radiation and size of radiation field.
    a. Mildly emetogenic: Radiation to the head and neck or to the extremities
    b. Moderately emetogenic: Radiation to the upper abdomen or pelvis or craniospinal radiation
    c. Highly emetogenic: Total body irradiation, total nodal irradiation, and upper-half-body irradiation

C. General Principles for Managing CINV and Radiation-Induced Nausea and Vomiting
1. Prevention is the key. Prophylactic antiemetics should be administered before moderately or highly emetogenic agents and before moderately and highly emetogenic radiation.
2. Antiemetics should be scheduled for delayed nausea and vomiting for select chemotherapy regimens (e.g., cisplatin, doxorubicin/cyclophosphamide (AC)), and rescue antiemetics should be available if prolonged acute symptoms or ineffective antiemetic prophylaxis occurs.
3. Patients need to be protected throughout the full period of risk for nausea/vomiting:
    a. 3 days for highly emetogenic regimens
    b. 2 days for moderately emetogenic regimens
4. Begin with an appropriate antiemetic regimen based on the emetogenicity of the chemotherapy drugs.
    a. For multidrug regimens, select antiemetic therapy according to the drug with the highest emetic risk.
    b. The most common antiemetic regimen for highly emetogenic chemotherapy and radiation is the combination of a neurokinin 1 (NK1) receptor antagonist, a serotonin receptor antagonist, and dexamethasone. Adding a corticosteroid to a serotonin receptor antagonist for highly (or moderately) emetogenic anticancer therapy increases efficacy by 10%–20%. Based on randomized clinical trial data, the AC regimen (see Table 1) should always include a three-drug regimen with an NK1 receptor antagonist, a serotonin receptor antagonist, and dexamethasone.
    c. Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines now recommend a four drug regimen for highly emetogenic chemotherapy to include a neurokinin 1 receptor antagonist, a serotonin receptor antagonist, dexamethasone, and olanzapine as the preferred prophylactic regimen. The standard three-drug regimen is still recommended as an option for highly emetogenic chemotherapy.
    d. For moderately emetogenic chemotherapy, the most common antiemetic regimen now includes a serotonin receptor antagonist and dexamethasone. Addition of an NK1 receptor antagonist may be considered after risk stratification.
    e. Single-agent phenothiazine, butyrophenone, or steroids are used for mildly emetogenic regimens and are given on either a scheduled or an as-needed basis for prolonged symptoms (i.e., breakthrough symptoms). Olanzapine is now a preferred option for breakthrough treatment.
    f. Consider using a histamine-2 blocker or proton pump inhibitor for dyspepsia (which can mimic nausea).
    g. Cannabinoids are generally used after other regimens have failed.
    h. Potential drug interactions between antineoplastic agents or antiemetics and other drugs should always be considered. However, no clinically significant drug-drug interactions have emerged to date in randomized clinical trials of anticancer agents with antiemetics. This is likely because of the short duration of antiemetic use in this population.
    i. Follow-up is essential. The response to the emetogenic regimen should always guide the choice of antiemetic regimen for subsequent therapy courses.

D. Emetogenic Potential of Parenteral Chemotherapy Agents

Table 1. Emetogenic Potential of Parenteral Chemotherapy Agents (per NCCN guidelines)

High Emetic Risk (> 90% frequency of emesis)	
AC (combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide)	Doxorubicin ≥ 60 mg/m^2
Carboplatin AUC ≥ 4	Epirubicin > 90 mg/m^2
Carmustine > 250 mg/m^2	Ifosfamide ≥ 2 g/m^2/dose
Cisplatin	Mechlorethamine
Cyclophosphamide > 1500 mg/m^2	Melphalan > 140 mg/m^2
Dacarbazine	Sacituzumab govitecan-hziy
	Streptozocin
Moderate Emetic Risk (30%–90% frequency of emesis)	
Aldesleukin > 12–15 million IU/m^2	Dual-drug liposomal encapsulation of cytarabine and daunorubicin
Amifostine > 300 mg/m^2	Epirubicin ≤ 90 mg/m^2
Azacitidine	Fam-trastuzumab deruxtecan
Bendamustine	Idarubicin
Busulfan	Ifosfamide < 2 g/m^2/dose
Carboplatin AUC < 4	Irinotecan
Carmustine ≤ 250 mg/m^2	Irinotecan (liposomal)
Clofarabine	Lurbinectedin
Cyclophosphamide ≤ 1500 mg/m^2	Melphalan < 140 mg/m^2
Cytarabine > 200 mg/m^2	Methotrexate ≥ 250 mg/m^2
Dactinomycin	Oxaliplatin
Daunorubicin	Temozolomide
Dinutuximab	Trabectedin
Doxorubicin < 60 mg/m^2	
Low Emetic Risk (10%–30% frequency of emesis)	
Ado-trastuzumab emtansine	Ixabepilone
Aldesleukin ≤ 12 million IU/m^2	Methotrexate > 50 mg/m^2 to < 250 mg/m^2
Amifostine ≤ 300 mg/m^2	Mitomycin and mitomycin pyelocalyceal solution
Arsenic trioxide	Mitoxantrone
Axicabtagene ciloleucel	Mogamulizumab
Belinostat	Moxetumomab
Brexucabtagene autoleucel	Necitumumab
Brentuximab vedotin	Olaratumab
Cabazitaxel	Omacetaxine
Carfilzomib	Paclitaxel
Copanlisib	Paclitaxel/albumin
Cytarabine (low dose) 100–200 mg/m^2	Pemetrexed
Docetaxel	Pentostatin
Doxorubicin (liposomal)	Polatuzumab vedotin
Enfortumab vedotin-ejfv	Pralatrexate
Eribulin	Romidepsin
Etoposide	Tafasitamab-cxix
Floxuridine	Tagraxofusp
Fluorouracil (5-FU)	Talimogene laherparepvec
Gemcitabine	Thiotepa
Gemtuzumab ozogamicin	Tisagenlecleucel
Inotuzumab ozogamicin	Topotecan
Isatuximab-irfc	Ziv-aflibercept

Table 1. Emetogenic Potential of Parenteral Chemotherapy Agents (per NCCN guidelines) *(Cont'd)*

Minimal Emetic Risk (< 10% frequency of emesis)	
Alemtuzumab	Nelarabine
Atezolizumab	Nivolumab
Asparaginase	Obinutuzumab
Avelumab	Ofatumumab
Bevacizumab	Panitumumab
Bleomycin	Pegaspargase
Blinatumomab	Pembrolizumab
Bortezomib	Pertuzumab
Cemiplimab	Pertuzumab/trastuzumab and hyaluronidase-zzxf
Cetuximab	Ramucirumab
Cladribine	Rituximab
Cytarabine < 100 mg/m^2	Rituximab and hyaluronidase human injection for subcutaneous use
Daratumumab	Siltuximab
Daratumumab and hyaluronidase-fihj	Temsirolimus
Decitabine	Trastuzumab
Denileukin diftitox	Trastuzumab and hyaluronidase injection for subcutaneous use
Dexrazoxane	Valrubicin
Durvalumab	Vinblastine
Elotuzumab	Vincristine
Fludarabine	Vincristine (liposomal)
Ipilimumab	Vinorelbine
Luspatercept-aamt	
Methotrexate ≤ 50 mg/m^2	

E. Emetogenic Potential of Oral Chemotherapy Agents (Table 2)

Table 2. Emetogenic Potential of Oral Chemotherapy Agents (per NCCN guidelines)

Moderate to High Emetic Risk (≥ 30% frequency of emesis); Prophylaxis Recommended	
Altretamine	Etoposide
Avapritinib	Fedratinib
Azacytidine	Imatinib > 400 mg/day
Binimetinib	Lenvatinib > 12 mg/day
Bosutinib > 400 mg/day	Lomustine (single day)
Busulfan ≥ 4 mg/day	Midostaurin
Capmatinib	Mitotane
Ceritinib	Niraparib
Crizotinib	Olaparib
Cyclophosphamide ≥ 100 mg/m^2/day	Procarbazine
Dabrafenib	Rucaparib
Enasidenib	Selinexor
Encorafenib	Temozolomide > 75 mg/m^2/day
Estramustine	

Table 2. Emetogenic Potential of Oral Chemotherapy Agents (per NCCN guidelines) *(Cont'd)*

Minimal to Low Emetic Risk (< 30% frequency of emesis); As Needed	
Abemaciclib	Melphalan
Acalabrutinib	Mercaptopurine
Afatinib	Methotrexate
Alectinib	Neratinib
Alpelisib	Nilotinib
Axitinib	Osimertinib
Bexarotene	Palbociclib
Bosutinib ≤ 400 mg/day	Panobinostat
Brigatinib	Pazopanib
Busulfan < 4 mg/day	Pemigatinib
Cabozantinib	Pexidartinib
Capecitabine	Pomalidomide
Chlorambucil	Ponatinib
Cobimetinib	Pralsetinib
Cyclophosphamide < 100 mg/m^2/day	Regorafenib
Dacomitinib	Ribociclib
Dasatinib	Ripretinib
Decitabine and cedazuridine	Ruxolitinib
Duvelisib	Selpercatinib
Entrectinib	Sonidegib
Erdafitinib	Sorafenib
Erlotinib	Sunitinib
Everolimus	Talazoparib tosylate
Fludarabine	Tazemetostat
Gefitinib	Temozolomide ≤ 75 mg/m^2/day
Gilteritinib	Thalidomide
Glasdegib	Thioguanine
Hydroxyurea	Topotecan
Ibrutinib	Trametinib
Idelalisib	Tretinoin
Imatinib ≤ 400 mg/day	Trifluridine/tipiracil
Ivosidenib	Tucatinib
Ixazomib	Vandetanib
Lapatinib	Vemurafenib
Larotrectinib	Venetoclax
Lenalidomide	Vismodegib
Lenvatinib ≤ 12 mg/day	Vorinostat
Lorlatinib	Zanubrutinib

F. Antiemetics
   1. Serotonin-3 receptor antagonists (dolasetron, granisetron, ondansetron, and palonosetron)
      a. Mechanism of action (MOA): Block serotonin receptors peripherally in the gastrointestinal tract and centrally in the medulla
      b. Adverse events: Headache and constipation, occurring in 10%–15% of patients. May increase liver function tests and cause QT prolongation (especially with high dosages or intravenous push administration).
      c. Dolasetron, granisetron, ondansetron, and palonosetron are considered equally efficacious at equivalent dosages. Therefore, the antiemetic drug of choice is often based on cost and organizational contract.

d. Dosage forms: Granisetron and ondansetron are available in oral and parenteral forms (including an orally disintegrating tablet for ondansetron). Dolasetron is now indicated only in CINV in its oral form. Granisetron is also available in a transdermal patch (34.3 mg applied about 24–48 hours before the first dose of chemotherapy; maximal duration of patch is 7 days) as well as an extended-release subcutaneous formulation (10 mg at least 30 minutes before first dose of chemotherapy; not to be administered more often than every 7 days).
e. Palonosetron is indicated to prevent acute CINV for highly emetogenic chemotherapy and acute and delayed CINV for moderately emetogenic chemotherapy.
    i. Half-life: About 40 hours (longer compared with other serotonin antagonists)
    ii. Dosage: 0.25 mg intravenous push 30 minutes before chemotherapy administration
    iii. An oral capsule form is available but only as a combination product with an NK1 antagonist (netupitant/palonosetron).
    iv. One dose may be used before the start of a 3-day chemotherapy regimen instead of several daily doses of oral or parenteral serotonin-3 receptor antagonists.
    v. Adverse events: Headache and constipation (same as other serotonin antagonists)

2. Corticosteroids (dexamethasone, methylprednisolone)
    a. MOA: Unknown; thought to act by inhibiting prostaglandin synthesis in the cortex
    b. Adverse effects associated with single doses and short courses of steroids are infrequent; they may include euphoria, anxiety, insomnia, increased appetite, and mild fluid retention; rapid parenteral administration may be associated with transient and intense perineal, vaginal, or anal burning.
    c. Dexamethasone has been studied more often in clinical trials than methylprednisolone.
    d. Corticosteroid antiemetic premedication should be avoided with immune checkpoint inhibitors when administered without cytotoxic chemotherapy.
    e. Corticosteroid antiemetic premedication should be avoided for 3–5 days before and 90 days after CAR (chimeric antigen receptor) T-cell therapies. Antiemetic regimens used during lymphodepleting chemotherapy regimens should also use a corticosteroid-sparing approach to antiemetic prophylaxis.
3. NK1 receptor antagonists (aprepitant, aprepitant injectable emulsion, fosaprepitant, rolapitant)
    a. All NK1 receptor antagonists must be used in combination with a serotonin receptor antagonist and dexamethasone and are approved for preventing acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy known to cause these problems, including highly emetogenic chemotherapy.
    b. MOA: Aprepitant is a selective high-affinity antagonist of human substance P/NK1.
    c. Aprepitant improved the overall complete response (defined as no emetic episodes and no use of rescue therapy) by about 20% when added to a serotonin receptor antagonist and dexamethasone.
    d. Aprepitant oral dosage: 125 mg on day 1, then 80 mg on day 2 and 80 mg on day 3. Intravenous aprepitant dosing is 130 mg on day 1 only for highly emetogenic chemotherapy and 100 mg on day 1 only for moderately emetogenic chemotherapy.
    e. Fosaprepitant dosage (prodrug): 150 mg intravenously on day 1 only (parenteral formulation)
    f. Metabolized primarily by cytochrome P450 (CYP) 3A4 (all NK1 agents), with aprepitant and fosaprepitant having minor metabolism by CYP1A2 and CYP2C19
        i. Dexamethasone: Fosaprepitant and aprepitant may increase area under the curve of dexamethasone. Decrease dosage by about 40% on day 2 or 3 if dexamethasone given orally (not necessary if given intravenously because of first-pass metabolism). Rolapitant does not inhibit dexamethasone metabolism.
        ii. Oral contraceptives: May reduce the effectiveness of oral contraceptives. Would recommend another form of birth control for women of childbearing age when taking with aprepitant/fosaprepitant

iii. Warfarin: May decrease international normalized ratio (clinically significant). After receiving fosaprepitant or aprepitant, patients should have their international normalized ratios checked within 7–10 days.
iv. Caution NK1 use in patients with lymphoma: Studies suggest neuropathy is more common in patients on R-CHOP receiving aprepitant, because of aprepitant's CYP3A4 inhibition. Other NK1 agents have CYP3A4 inhibition, and caution should be used with these as well.

g. Adverse events: Asthenia, dizziness, and hiccups
h. MOA: Rolapitant substance P/NK1 receptor antagonist indicated in combination with dexamethasone and serotonin antagonist in adults with cancer for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy.
i. Rolapitant dosage: 180 mg orally on day 1 only
j. Adverse events: Loss of appetite, neutropenia, and hiccups

4. NK1 receptor antagonist/serotonin-3 combination (netupitant/palonosetron and fosnetupitant/palonosetron)
   a. MOA: Fixed combination of netupitant/fosnetupitant, a substance P/NK1 receptor antagonist, and palonosetron, a serotonin-3 receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase, and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phases after cancer chemotherapy.
   b. Netupitant/palonosetron dosage: 1 capsule once on day 1 (capsule contains 300 mg of netupitant/palonosetron 0.5 mg)
   c. Fosnetupitant/palonosetron dosage: Intravenously once daily on day 1 (contains 235 mg of fosnetupitant/palonosetron 0.25 mg)
   d. Adverse effects: Headache, asthenia, dyspepsia, fatigue, constipation, and erythema
   e. Caution in patients with hepatic dysfunction, severe renal impairment, or end-stage renal disease
5. Benzamide analogs (metoclopramide)
   a. MOA: Blockade of dopamine receptors in the chemoreceptor trigger zone; stimulation of cholinergic activity in the gut, increasing (forward) gut motility; and antagonism of peripheral serotonin receptors in the intestines. These effects are dose related.
   b. Adverse events: Mild sedation and diarrhea, as well as extrapyramidal reactions (e.g., dystonia, akathisia), which may be mitigated by diphenhydramine or benztropine.
   c. Historically, higher dosages of metoclopramide were used for desired results (1–2 mg/kg intravenously). Guidelines now recommend 10–20 mg every 6 hours, if needed.
6. Phenothiazines (prochlorperazine, chlorpromazine, promethazine)
   a. MOA: Block dopamine receptors in the chemoreceptor trigger zone
   b. Adverse events: Drowsiness, hypotension, akathisia, and dystonia
7. Butyrophenones (haloperidol, droperidol)
   a. MOA: Similar to phenothiazines
   b. They are at least as effective as the phenothiazines, and some studies indicate they are superior; they offer a different chemical structure that may bind differently to the dopamine receptor and offer an initial alternative when a phenothiazine fails.
   c. Adverse events: Sedation; hypotension is less common than with phenothiazines; extrapyramidal symptoms are also seen.
   d. The use of droperidol as an antiemetic has fallen out of favor because of the risk of QT prolongation or torsades de pointes.

8. Benzodiazepines (lorazepam)
    a. Lorazepam as a single agent has minimal antiemetic activity. However, several properties make lorazepam useful in combination with or as an adjunct to other antiemetics.
        i. Anterograde amnesia helps prevent anticipatory nausea and vomiting.
        ii. Relief of anxiety
        iii. Management of akathisia caused by phenothiazines, butyrophenones, or metoclopramide
        iv. Adverse events: Amnesia, sedation, hypotension, perceptual disturbances, and urinary incontinence. Note that amnesia and sedation may, in fact, be desirable.
9. Atypical antipsychotic (olanzapine)
    a. Approved by the U.S. Food and Drug Administration (FDA) to treat schizophrenia and bipolar disorder, this thienobenzodiazepine is used off label as an alternative agent for preventing nausea and vomiting in highly emetogenic regimens and may be used as an option for breakthrough nausea and vomiting.
    b. MOA: Blocks multiple neurotransmitters, including dopamine, serotonin, catecholamines, acetylcholine, and histamine
    c. Adverse effects: Sedation, dry mouth, increased appetite, weight gain, postural hypotension, QTc prolongation, and dizziness
    d. Olanzapine has been associated with an elevated risk of hyperlipidemia, hyperglycemia, and new-onset diabetes. Use with caution in older adults because olanzapine use in this patient population has been associated with an elevated risk of death and an elevated incidence of cerebrovascular adverse events in patients with dementia-related psychosis (black box warning)
    e. A phase III study compared olanzapine with aprepitant in highly emetogenic chemotherapy regimens. Overall response rates were similar in both groups for acute and delayed nausea and vomiting. The proportion of patients without nausea was similar between the two groups in the acute period but was higher in the olanzapine arm in the delay period, resulting in a higher rate of nausea control. As an alternative to, or in combination with, aprepitant, an olanzapine-based regimen is an option in highly or moderately emetogenic regimens according to the most recent National Comprehensive Cancer Network (NCCN) guidelines.
10. Cannabinoids (dronabinol, nabilone)
    a. MOA: Cannabinoid receptors may mediate at least some of the antiemetic activity of this class of agents. Additional antiemetic mechanisms that have been proposed include inhibition of prostaglandins and blockade of adrenergic activity.
    b. Adverse events: Drowsiness, dizziness, euphoria, dysphoria, orthostatic hypotension, ataxia, hallucinations, and time disorientation

G. Emesis Prevention Algorithms (Tables 3 and 4)

Table 3. Emesis Prevention Algorithm for Parenteral Chemotherapy (per NCCN Guidelines)[a]

Level of Emetogenicity	Emesis Treatment Day 1	Emesis Treatment Days 2, 3, and 4
High	NK1 antagonist - Aprepitant 125 mg PO once - Aprepitant injectable emulsion 130 mg IV once - Fosaprepitant 150 mg IV once - Netupitant 300 mg/palonosetron 0.5 mg combination PO once - Fosnetupitant 235 mg/palonosetron 0.25 mg combination IV once - Rolapitant 180 mg PO once AND Serotonin-3 antagonist AND Dexamethasone 12 mg PO/IV once ± Olanzapine 5–10 mg PO once ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	- Aprepitant 80 mg PO daily on days 2 and 3 (only if aprepitant PO used on day 1) - Dexamethasone 8 mg PO/IV daily on days 2, 3, 4 - Olanzapine 5–10 mg PO daily on days 2, 3, 4 (if olanzapine PO used on day 1)
	OR	OR
	Olanzapine-containing regimen: 1. Olanzapine 5–10 mg PO 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	Olanzapine 5–10 mg PO days 2–4

[a]A four-drug regimen containing an NK1 antagonist, a serotonin antagonist, dexamethasone, and olanzapine is now the preferred first-line prophylactic option for highly emetogenic regimens according to the most recent NCCN and ASCO antiemetic guidelines.

Table 3. Emesis Prevention Algorithm for Parenteral Chemotherapy (per NCCN Guidelines) *(Cont'd)*

Level of Emetogenicity	Emesis Treatment Day 1	Emesis Treatment Days 2 and 3
Moderate	Serotonin-3 antagonist AND Steroid - Dexamethasone 12 mg PO/IV once WITH/WITHOUT NK1 antagonist ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor OR Olanzapine-containing regimen: 1. Olanzapine 5–10 mg PO 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg IV once ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	Serotonin-3 antagonist OR Steroid monotherapy Dexamethasone 8 mg PO/IV daily on days 2, 3 OR - If aprepitant PO given day 1, aprepitant 80 mg PO daily on days 2, 3 ± dexamethasone 8 mg PO/IV days 2, 3 - If fosaprepitant given day 1, no further NK1 antagonists needed on days 2 and 3 ± dexamethasone days 2, 3 - If rolapitant given day 1, no further NK1 antagonists needed on days 2, 3 ± dexamethasone days 2, 3 OR Olanzapine-containing regimen: Olanzapine 5–10 mg PO days 2, 3
Low	Dexamethasone 8-12 mg PO/IV once OR Metoclopramide 10-20 mg PO/IV once OR Prochlorperazine 10 mg PO/IV once OR Serotonin-3 antagonists (oral therapy) ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor	Repeat day 1 selection daily for multi-day doses of chemotherapy only
Minimal	No routine prophylaxis	No routine prophylaxis

IV = intravenous(ly); NK1 = neurokinin 1; PO = orally.

Table 4. Emesis Prevention Algorithm for Oral Chemotherapy per NCCN Guidelines

Level of Emetogenicity	Emesis Treatment (start before chemotherapy and continue daily)
Moderate to high emetic risk	Serotonin-3 antagonist (choose one): Dolasetron 100 mg daily Granisetron 1–2 mg (total dose) PO daily or 3.1 mg/24-hr transdermal patch every 7 days Ondansetron 8-16 mg PO daily ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor
Minimal to low emetic risk	Metoclopramide 10–20 mg PO and then q6hr PRN OR Prochlorperazine 10 mg PO and then q6hr PRN (maximum 40 mg/day) OR Serotonin-3 antagonist (choose one): Dolasetron 100 mg PO daily PRN Granisetron 1-2 mg (total dose) PO daily PRN Ondansetron 8–16 mg PO daily PRN ± Lorazepam ± Histamine-2 blocker or proton pump inhibitor

BID = twice daily; PRN = as needed; q = every.

Patient Case

Questions 1 and 2 pertain to the following case.

A 60-year-old woman was recently given a diagnosis of advanced non–small cell lung cancer. She will begin treatment with cisplatin 100 mg/m^2 plus vinorelbine 30 mg/m^2.

1. Which is the most appropriate antiemetic regimen for preventing acute emesis?
   A. Aprepitant plus palonosetron plus dexamethasone.
   B. Aprepitant plus prochlorperazine plus dexamethasone.
   C. Aprepitant plus granisetron plus ondansetron.
   D. Lorazepam plus ondansetron plus metoclopramide.

2. If the patient has anticipatory nausea and vomiting with her next cycle, which regimen would be most appropriate?
   A. Aprepitant plus palonosetron plus dexamethasone.
   B. Aprepitant plus prochlorperazine plus dexamethasone.
   C. Aprepitant plus granisetron plus metoclopramide.
   D. Aprepitant plus ondansetron plus dexamethasone plus lorazepam.

II. PAIN MANAGEMENT

A. Principles of Cancer Pain Management
   1. The most important step in treating pain is the assessment.
   2. The oral route is preferred, when available. Although the ratio of oral to parenteral potency of morphine is commonly 6:1, clinical observation of chronic morphine use indicates that this ratio is closer to 3:1.
   3. Choose the analgesic drug and dosage to match the patient's degree of pain.
   4. For persistent severe pain, use a product with a long duration of action. Pain medications should always be administered on a scheduled basis or around the clock, not as needed.
      a. It is always easier to prevent pain from recurring than to treat it once it has recurred.
      b. As-needed dosing should be used for breakthrough pain, which is pain that "breaks through" the regularly scheduled opioid; an immediate-release, short-acting opioid should always accompany a long-acting opioid.
   5. Reevaluate pain and pain relief often, especially when initiating pain therapy; if more than two as-needed doses are necessary for breakthrough pain in a 24-hour period, consider modifying the regimen. Before adding or changing to another drug, maximize the dosage and schedule of the current analgesic drug.
   6. Provide medications to prevent other potential side effects from opioid therapy (e.g., constipation).
   7. Use appropriate adjuvant analgesics and nondrug measures to maximize pain control.
   8. Goals of pain management (The "5 A's")
      a. Optimize analgesia.
      b. Optimize activities of daily living.
      c. Minimize adverse effects.
      d. Avoid aberrant drug taking.
      e. Relationship between pain and mood (affect)
   9. Survival is linked to symptom control and pain management, which contribute to broad quality-of-life improvement.
   10. For acute, severe pain or pain crisis, consider hospital or inpatient hospice admission.

B. Diagnosis and Assessment of Pain
   1. Best addressed by proper pain assessment including comprehensive history and physical examination
   2. Evaluation of pain management: Pain intensity, pain relief, and medication adverse effects or allergies must be assessed and reassessed.
   3. Objective observations such as grimacing, limping, or tachycardia may be helpful in assessment.
   4. Clinicians must accept the patient's report of pain.

C. Pain Rating Scales
   1. Use pain assessment tools to evaluate pain intensity at baseline and to assess how well a pain medication regimen is working.
      a. Numeric rating scale of 0–10, with 0 = no pain and 10 = worst pain imaginable
      b. Pediatric patients: Faces-of-Pain Scale, poker chip method
   2. Because pain is subjective, it is best evaluated by the patient (i.e., not a caregiver and not the health professional).

D. Treatment of Pain: The Analgesic Ladder
   1. For mild pain (pain rating of 1–3 on a 10-point scale), the first step is a nonopioid analgesic drug: Nonsteroidal anti-inflammatory drug (NSAID), aspirin, or acetaminophen, or consider slow titration of short-acting opioids either as needed or as scheduled.

2. For persistent or moderate pain (pain rating of 4–7 on a 10-point scale), add a weak opioid: Codeine or hydrocodone, available in combination with nonopioid analgesic drugs. Slow titration of a short-acting opioid may also be considered.
3. For persistent or for severe pain (pain rating of 8 or greater on a 10-point scale), replace the weak opioid with a strong opioid: Morphine, oxycodone, or similar drug. In opioid-naive patients experiencing severe pain, short-acting opioids should be rapidly titrated. Once a patient with persistent pain is taking stable dosages of short-acting opioids, the drug should be changed to an extended-release or long-acting formulation with breakthrough short-acting opioids.

E. Nonopioid Analgesics: NSAIDs
1. MOA: Act peripherally to inhibit the activity of prostaglandins in the pain pathway
2. There is a ceiling effect to the analgesia provided by NSAIDs.
3. Adverse events: Consider inhibition of platelet aggregation and the effects of inhibition of renal prostaglandins. NSAIDs in patients with hematologic disorders are generally not recommended because of platelet inhibition. In addition, there are concerns about the possibility that NSAIDs will mask fever in a patient with neutropenia who is potentially febrile.
4. Remember, NSAIDs are generally used in addition to, not instead of, opioids.
5. NSAIDs are often used for patients with metastatic bone pain.

F. Nonopioid/Opioid Combinations
1. Aspirin or acetaminophen or ibuprofen plus codeine or hydrocodone or oxycodone is commonly used.
2. Be aware of the risk of acetaminophen overdose with these products. As with any combination product, dosage escalation of one component necessitates escalation of the others. For patients needing high dosages, pure opioids are preferred.
3. Oxycodone/acetaminophen is available in several strengths; however, use caution when taking multiple tablets per day because of the acetaminophen daily maximum recommendations.

G. Opioid Analgesics
1. Mechanism: Opioids act centrally in the brain (periaqueductal gray region) and at the level of the spinal cord (dorsal horn) at specific opioid receptors.
2. The opioids have no analgesic ceiling.
3. Morphine
    a. Morphine is the standard with which all other drugs are compared; opioids may differ in duration of action, relative potency, oral effectiveness, and adverse event profiles, but none is clinically superior to morphine.
    b. Flexibility in dosage forms and administration routes: Oral (sustained release, immediate release), sublingual, parenteral, intrathecal/epidural, subcutaneous, and rectal
    c. Long duration of action: Sustained-release products last 8–12 hours or, for some preparations, 24 hours.
    d. Morphine is one of the least expensive opioids, but it should be used with caution in patients with renal dysfunction because of the metabolite.
4. Oxycodone
    a. Available in oral formulation only
    b. Available as a single drug (i.e., not in combination) in both long- and short-acting formulations
    c. Alternative to morphine in the setting of renal dysfunction
5. Fentanyl
    a. Fentanyl is available as a parenteral formulation; a sublingual, intranasal, or transdermal preparation; an oral transmucosal preparation; and a buccal tablet. Transmucosal and buccal fentanyl are used for breakthrough pain.

   b. Each transdermal patch provides sustained release of drug and can provide pain relief for 48–72 hours. These should not be used in opioid-naive patients.
   c. Consider the implications for dosing transdermal fentanyl in cachectic patients: Fentanyl initially forms a depot in subcutaneous tissue, and patients with little or no fat may not achieve pain relief or may achieve only inconsistent pain relief.
   d. Slow onset and long elimination after patch application and removal, respectively
   e. Bioavailability is greater with buccal tablets than with the transmucosal preparation; thus, equivalent dosages are higher for transmucosal and lower for buccal tablets.
6. Hydromorphone
   a. Available in parenteral and oral formulations (short- and long-acting)
   b. Considered a semisynthetic compound
   c. Alternative to morphine with higher potency
   d. Alterative option in patients with renal dysfunction
7. Oxymorphone
   a. Semisynthetic opioid analgesic
   b. Most commonly seen as immediate- and extended-release tablets
   c. Used for moderate to severe pain
   d. Should not be implemented in patients who are not currently on an opioid regimen
   e. On June 8, 2017, the FDA has requested that the extended-release formulation of oxymorphone be removed from the market because of risks related to abuse.
8. Methadone
   a. Semisynthetic used in maintenance treatment for opioid-dependent patients and as an effective analgesic in patients taking opioids long term for moderate to severe pain
   b. Has activity not only at the opioid receptors but also at the *N*-methyl-D-aspartate receptor, which may confer benefit to patients with neuropathic pain
   c. Complex pharmacokinetics with extended half-life (8–59 hours), which creates difficulties in dosing and transitioning from one opioid to another
   d. Associated with QT prolongation and torsades de pointes
   e. Start low and titrate slowly (only escalating after 3–5 days) because of the changing conversion ratios with increasing morphine equivalents.
9. Adverse events
   a. Sedation: Tolerance usually develops within several days; remember that more sedation may be expected in a patient who has been unable to sleep because of uncontrolled pain. For patients who are intolerant of sedation and have good pain control, a dosage reduction may be considered. If dosage reduction compromises pain control, adding a stimulant (e.g., dextroamphetamine, methylphenidate) may be considered. Other central nervous system adverse events include dysphoria and hallucinations.
   b. Constipation is very common, and tolerance does not develop to this effect. Decreased intestinal peristalsis is caused by decreased intestinal tone; delayed gastric emptying may also occur. Regular use of stool softeners in addition to a stimulant laxative is imperative to manage constipation.
   c. Nausea and vomiting are common. As seen with sedation, tolerance develops within about a week. Nausea and vomiting may have a vestibular component, developing as pain relief promotes increased mobility. Agents used in the treatment of vertigo (e.g., meclizine, dimenhydrinate) may be useful in managing the vestibular component, although these agents should be used with caution because combination use with opioids may increase sedation. Nausea and vomiting may also occur because of stimulation of the chemoreceptor trigger zone. Drugs that block dopamine receptors (e.g., phenothiazines) provide relief of this component of nausea and vomiting until tolerance develops.
   d. Urinary retention and bladder spasm are more common in older adults and in patients taking long-acting formulations.

H. Bisphosphonates
   1. Bisphosphonates decrease the worsening of pain by preventing disease progression in the bone and the number of skeletal-related events in patients with bone metastases from solid tumors or osteolytic lesions from multiple myeloma when given for 1 year. Skeletal-related events include pathologic fracture, need for radiation therapy to bone, surgery to bone, and spinal cord compression.
   2. Most recently updated in October 2017 the American Society of Clinical Oncology published initial guidelines for the use of bisphosphonates in breast cancer.
      a. It is recommended that patients with breast cancer who have evidence of bone metastases on plain radiographs receive either pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3–4 weeks. Dosage adjustments for renal dysfunction are necessary according to package insert recommendations.
      b. Women with abnormal bone scan and abnormal computed tomographic scan or magnetic resonance imaging showing bone destruction but a normal radiograph should also receive the previously recommended bisphosphonates.
      c. Therapy should continue until the patient has evidence of a substantial decline in performance status.
      d. Bisphosphonates may be used in combination with other pain therapies in patients with pain caused by osteolytic disease.
      e. A new guideline for adjuvant bisphosphonate use in breast cancer by the American Society of Clinical Oncology published in March 2017 recommends that zolendronic acid 4 mg over 15 minutes every 6 months be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy.
   3. Most recently updated in 2018, the American Society of Clinical Oncology published guidelines for the use of bisphosphonates in multiple myeloma.
      a. Patients with lytic bone destruction seen on plain radiographs should receive either pamidronate 90 mg intravenously over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3–4 weeks (dosing once every 3 months may be considered in patients with stable/responsive disease).
      b. Therapy should continue until there is evidence of substantial decline in a patient's performance status.
      c. Patients with osteopenia but no radiologic evidence of bone metastases or compression fracture can receive bisphosphonates.
      d. Bisphosphonates are not recommended for patients with solitary plasmacytoma, smoldering or indolent myeloma, or monoclonal gammopathy of undetermined significance.
      e. Bisphosphonates may be used in patients with pain caused by osteolytic disease.
   4. Standard dosing for bisphosphonates in solid tumor metastases is once every 3–4 weeks. However, recent data analyses have supported less-frequent dosing. Dosing once every 12 weeks did not increase the risk of skeletal events within 2 years in patients with at least one site of bone involvement compared with once-every-4-week dosing.
   5. Adverse events: Low-grade fevers, nausea, anorexia, vomiting, hypomagnesemia, hypocalcemia, hypokalemia, nephrotoxicity, and atypical femur fractures
      a. Serum creatinine should be monitored before each dose (see package insert for specific recommendations).
      b. Package insert recommends initiating patients on oral calcium 500 mg plus vitamin D 400 international units/day to prevent hypocalcemia.
      c. Several reports of osteonecrosis of the jaw occurring in patients receiving bisphosphonates have appeared in the literature. Osteonecrosis of the jaw usually follows a dental or dental disorder. The long half-life of bisphosphonates in bone makes this adverse event difficult to prevent and manage. Patient education and education of dentists are important. Patients should have a dental examination with preventive dentistry before treatment with bisphosphonates.

I. Receptor Activator of NF-κB Ligand (RANKL) Inhibitor
   1. Denosumab: Fully human monoclonal antibody that targets and inhibits RANKL, a protein that acts as the primary signal to promote bone removal
   2. Indication: Prevention of skeletal-related events in patients with bone metastases from solid tumors and in patients with multiple myeloma.
   3. Dosage: 120 mg subcutaneously every 4 weeks
   4. Adverse events: Urinary and respiratory tract infections, cataracts, constipation, rashes, hypocalcemia (especially in patients with CrCl less than 30 mL/minute), osteonecrosis of the jaw, and joint pain
   5. Contraindications: Hypocalcemia. Patients should be taking calcium and vitamin D.
   6. No adjustment for hepatic or renal dysfunction is needed.

J. Adjuvant analgesics are drugs whose primary indication is other than pain; they are used to manage specific pain syndromes. Most often, adjuvant analgesics are used in addition to, rather than instead of, opioids.
   1. Antidepressants (e.g., amitriptyline, duloxetine) and anticonvulsants (e.g., gabapentin, carbamazepine, pregabalin) are used for neuropathic pain (e.g., phantom limb pain, nerve compression caused by tumor).
   2. Transdermal lidocaine is useful in localized neuropathic pain.
   3. Corticosteroids are useful in pain caused by nerve compression or inflammation, lymphedema, bone pain, or elevated intracranial pressure.
   4. Benzodiazepines: Diazepam, lorazepam. Useful for muscle spasms; baclofen is another alternative for intractable muscle spasms
   5. Strontium-89: Radionuclide for treatment of bone pain caused by osteoblastic lesions; a single dose may provide relief for several weeks or even months; however, it is myelosuppressive.
   6. NSAIDs are recommended for treating pain caused by bone metastases. Prostaglandins sensitize nociceptors (pain receptors) to painful stimuli, thus providing a rationale for using NSAIDs.

K. Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release/Long-Acting Opioid Analgesics
   1. On June 9, 2012, the FDA announced it would require manufacturers of extended-release and long-acting opioid analgesics to provide training for health care professionals who prescribe these agents.
   2. Components of the REMS program
      a. Prescriber education: Information on extended-release or long-acting opioid analgesics; information on assessing patients for treatment with these drugs; initiating therapy, modifying dosing, and discontinuing use of extended-release or long-acting opioid analgesics; managing therapy and monitoring patients; and counseling patients and caregivers about the safe use of these drugs. Prescribers will also learn how to recognize evidence of potential opioid misuse, abuse, and addiction.
      b. Patient counseling: Patient counseling documents for providers will be developed to assist prescribers in counseling patients about their responsibilities for using these medications safely. Patients will receive an updated medication guide, together with their prescription, that contains information on the safe use and disposal of extended-release or long-acting opioid analgesics from their pharmacist. Guide will include instructions for patients to consult their health care professional before changing dosages, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure of family members.
      c. Short-acting opioid products are not included in this program.

Patient Case

Questions 3 and 4 pertain to the following case.

A 75-year-old man has metastatic prostate cancer. The main sites of metastatic disease are regional lymph nodes and bone (several hip lesions). He has aching pain with occasional shooting pains. The latter are thought to be the result of nerve compression by enlarged lymph nodes. He has been taking oxycodone/acetaminophen 5 mg/325 mg 2 tablets every 4 hours and ibuprofen 400 mg every 8 hours. His current pain rating is 8/10, and he states that his pain cannot be controlled.

3. Which is the best recommendation to manage his pain at this time?
   A. Increase oxycodone/acetaminophen to 7.5 mg/325 mg, 2 tablets every 4 hours.
   B. Increase oxycodone/acetaminophen to 10 mg/325 mg, 2 tablets every 4 hours.
   C. Discontinue oxycodone/acetaminophen, discontinue ibuprofen, and add morphine sustained release every 12 hours.
   D. Discontinue oxycodone/acetaminophen and add morphine sustained release every 12 hours.

4. Which is the most appropriate adjunctive medication for this patient's pain?
   A. Naproxen.
   B. Single-agent (single ingredient) acetaminophen.
   C. Gabapentin.
   D. Baclofen.

III. TREATMENT OF FEBRILE NEUTROPENIA

A. Principles of Chemotherapy-Induced Bone Marrow Suppression
   1. Bone marrow suppression is the most common dose-limiting toxicity associated with traditional cytotoxic chemotherapy.
   2. WBC = Usual range of 4.8–10.8 × 100 cells/mm^3 with a circulating life span of 6–12 hours; decreased WBC = leucopenia or granulocytopenia; the risk is life-threatening infections; the risk increases with absolute neutrophil count (ANC) less than 500 cells/mm^3, and the risk is greatest with ANC less than 100 cells/mm^3. Because neutrophils have the fastest turnover, the effects of cytotoxic chemotherapy are greatest on neutrophils (compared with platelets or red blood cells [RBCs]).
      a. The nadir (usually defined by the ANC) is the lowest value to which the blood count falls after cytotoxic chemotherapy. Usually occurs 10–14 days after chemotherapy administration, with counts usually recovering by 3–4 weeks after chemotherapy; exceptions include mitomycin, decitabine, azacitidine, bleomycin, vincristine, and nitrosoureas (carmustine and lomustine), which have nadirs of 28–42 days after chemotherapy and recovery of neutrophils 6–8 weeks after treatment
      b. General rule for calculating ANC: ANC = WBC × percentage granulocytes or neutrophils (segmented neutrophils plus band neutrophils). Example: A patient's WBC = 4500 cells/mm^3 with 10% segmented neutrophils and 5% band neutrophils. What is the ANC? 4500 × (0.1 + 0.05) = 675 cells/m^3.
      c. To receive chemotherapy, in general, a patient should have a WBC greater than 3000 cells/mm^3 or an ANC greater than 1000 cells/mm^3 and a platelet count of 100,000 cells/mm^3 or more. In some protocols, consideration of the patient's clinical status and FDA labels or package inserts specify different (lower) thresholds for administering chemotherapy; if cytopenia is attributable to disease in the bone marrow, chemotherapy (full dose) may in fact be indicated and will normalize cytopenia when disease improves with treatment; some drugs are nonmyelosuppressive (e.g., vincristine, bleomycin, monoclonal antibodies).

d. The potential curability of the disease influences what action will be taken during the next cycle of chemotherapy, either dosage reduction of myelosuppressive chemotherapy (palliative intent) or support with a CSF (curative intent). Exceptions to the use of CSFs in the curative setting exist because of potential toxicities with various regimens. Use of CSFs is usually avoided in Hodgkin lymphoma with the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen because various retrospective studies have found that patients receiving ABVD who develop neutropenia rarely develop infection complications and appear to have the potential for increased pulmonary toxicities with bleomycin if CSFs are used.

3. Other factors affecting myelosuppression include previous chemotherapy, previous radiation therapy, and direct bone marrow involvement by tumor. The development of rare blood disorders (e.g., thrombotic microangiopathy or disseminated intravascular coagulation) must be ruled out in patients with malignancies who received myelosuppressive chemotherapy but experienced an unexplained delay in recovery of platelets and hemoglobin.

B. Neutropenia and Febrile Neutropenia

1. Infectious Diseases Society of America guidelines for antibiotic use were updated in 2010.
2. Neutropenia is defined as an ANC of 500 cells/mm^3 or less or a count of less than 1000 cells/mm^3, with a predicted decrease to less than 500 cells/mm^3 during the next 48 hours.
3. Febrile neutropenia is defined as neutropenia and a single oral temperature of 101°F or more or a temperature of 100.4°F or more for at least 1 hour.
4. Neutropenic patients are at an elevated risk of developing serious and life-threatening infections.
5. The usual signs and symptoms of infection (e.g., abscess, pus, infiltrates on chest radiograph) are absent, with fever often being the only indicator. In addition, cultures are typically negative. Therefore, febrile neutropenia necessitates . . . prompt investigation and treatment.
6. Treatment of patients with febrile neutropenia includes a risk assessment for complications and severe infection.
   a. Characteristics of low-risk neutropenia include the following: ANC of 100 cells/mm^3 or more and absolute monocyte count of 100 cells/mm^3 or more, normal chest radiograph, almost normal renal and hepatic function, severe neutropenia (100 cells/mm^3 or less) for less than 7 days and resolution expected in less than 10 days, no parenteral access site or catheter site infection, early evidence of bone marrow recovery, malignancy in remission, peak oral temperature of less than 102°F, no neurologic or mental status changes, no appearance of illness, absence of abdominal pain, and no comorbid complications (e.g., shock, hypoxia, pneumonia, other deep organ infection, vomiting, diarrhea).
   b. The Multinational Association for Supportive Care in Cancer has developed a scoring index to help identify patients with low-risk febrile neutropenia. Scores are assessed on the basis of factors such as those listed previously. A MASCC risk index score of less than 21 indicates high-risk febrile neutropenia, whereas a score of 21 or greater indicates low-risk febrile neutropenia.
   c. The Clinical Index of Stable Febrile Neutropenia (CISNE) provides another risk categorization for risk of serious complications, including mortality in patients with neutropenic fever. Risk stratification is validated in adults. A CISNE score of 3 or greater indicates high-risk febrile neutropenia, and a score of less than 3 indicates low-risk febrile neutropenia.
   d. Febrile neutropenia that is considered to carry a low risk of complications may be treated with either oral or parenteral antibiotics in an outpatient or inpatient setting.
   e. Patients with high-risk febrile neutropenia (i.e., patients who do not have low-risk characteristics, as noted earlier) should receive parenteral antibiotics in the hospital.

7. Considerations in the initial selection of an antibiotic include the potential infecting organism, potential sites and source of infection, local antimicrobial susceptibilities, and organ dysfunction potentially affecting antibiotic clearance or toxicity, and drug allergy. The most common source of infection is endogenous flora, which could be gram-negative or gram-positive bacteria; the more prolonged the neutropenia (and the more prolonged the administration of antibacterial antibiotics), the greater chance of fungi playing a role in the infection.
8. Recommendations for initial empiric treatment for patients with high-risk febrile neutropenia include broad-spectrum monotherapy with an antipseudomonal β-lactam such as cefepime, a carbapenem, or piperacillin/tazobactam.
9. Parenteral combination therapy can be considered (aminoglycosides, fluoroquinolones, and/or vancomycin), especially for management of complications (e.g., hypotension and pneumonia) or if antimicrobial resistance is expected.
10. Vancomycin is not recommended as standard initial therapy in patients with febrile neutropenia but may be considered for combination therapy with an antipseudomonal β-lactam for the following: sepsis (hemodynamic instability); pneumonia (radiographic evidence); positive blood culture for gram-positive bacteria; catheter-related infection; skin or soft tissue infection; colonization with methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, or penicillin-resistant Streptococcus pneumoniae; or severe mucositis (if fluoroquinolone prophylaxis used).
11. All patients should be reassessed after 3–5 days of antibiotic therapy, and antibiotics should be adjusted accordingly. Empiric antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics whose overall duration of neutropenia is expected to be more than 7 days.
12. Prophylactic antibiotics (fluoroquinolones, trimethoprim/sulfamethoxazole) may be considered for patients who are receiving chemotherapy who are expected to be profoundly neutropenic for more than 7 days.

IV. USE OF COLONY-STIMULATING FACTORS FOR PREVENTION OF FEBRILE NEUTROPENIA

A. CSFs improve both the production and the function of their target cells. Four products and five biosimilars are currently available in the United States: Granulocyte colony-stimulating factor (G-CSF, or filgrastim [Neupogen]) or tbo-filgrastim (Granix), pegylated granulocyte colony-stimulating factor (PEG-G-CSF, pegfilgrastim [Neulasta]) granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]). The biosimilars are filgrastim-sndz (Zarxio), filgrastim-aafi (Nivestym), pegfilgrastim-bmez (Ziextenzo), pegfilgrastim-cbqv (Udenyca), and pegfilgrastim-jmdb (Fulphila).

B. Pegfilgrastim, the long-acting agent, and the biosimilars pegfilgrastim-bmez, pegfilgrastim-cbqv, and pegfilgrastim-jmdb are approved for use in patients with nonmyeloid malignancies who are receiving myelosuppressive chemotherapy associated with a high incidence of febrile neutropenia.

C. Studies have shown that G-CSF and GM-CSF reduce the incidence, magnitude, and duration of neutropenia after chemotherapy and bone marrow transplantation.

D. Guidelines for the use of CSFs were established by the American Society of Clinical Oncology in 1994; the most recent update was published in 2015.

E. CSFs are recommended for primary prophylaxis with chemotherapy regimens associated with a 20% or greater risk of febrile neutropenia.
   1. G-CSF, tbo-filgrastim, GM-CSF, filgrastim-sndz, and filgrastim-aafi are all dosed at 5 mcg/kg and are given by daily subcutaneous injection.
   2. To date, no large trials have compared G-CSF and GM-CSF. Therefore, although it cannot be stated unequivocally that the two are therapeutically equivalent, they are often used interchangeably. However, they have varying adverse effect profiles (increased in fluid retention and fevers with GM-CSF).
   3. A meta-analysis of tbo-filgrastim and filgrastim resulted in tbo-filgrastim being noninferior to filgrastim for reducing the incidence of febrile neutropenia. Toxicities are considered similar between the two agents.
   4. Pegfilgrastim is given as a single 6-mg subcutaneous dose, generally administered 24–72 hours after chemotherapy. Pegfilgrastim on-body injector is also available for administration in the outpatient setting. The on-body single use injector can be applied on the same day of chemotherapy, but it is designed to deliver the actual dose the next day about 27 hours later.
   5. A single dose of pegfilgrastim is as effective as 11 daily doses of G-CSF 5 mcg/kg in reducing the frequency and duration of severe neutropenia, promoting neutrophil recovery, and reducing the frequency of febrile neutropenia. After a dose of pegfilgrastim is administered, chemotherapy should not be given for 10–14 days.
   6. Tbo-filgrastim was approved in an original biologics license application by the FDA in 2012. The FDA has not approved tbo-filgrastim as a biosimilar to Neupogen (filgrastim).
   7. Filgrastim-sndz was the first biosimilar approved by the FDA (March 2015). Filgrastim-aafi was FDA approved in July 2018 as another biosimilar option to filgrastim.
   8. The choice of CSF (pegfilgrastim vs. filgrastim) should be based on the expected duration of neutropenia and the specific anticancer regimen (e.g., short courses of a daily CSF rather than one dose of pegfilgrastim) with chemotherapy administration on a weekly schedule.
   9. Adverse events associated with all three preparations appear similar; they include bone pain (most common) and fever.
   10. The CSF should be initiated 24–72 hours after the completion of chemotherapy.
   11. The package literature recommends continued administration of G-CSF until the post-nadir ANC is greater than 10,000 cells/mm^3; however, both G-CSF and GM-CSF are usually discontinued when adequate neutrophil recovery is evident. To decrease cost without compromising patient outcome, many centers continue the CSF until ANC is greater than 2000–5000 cells/mm^3. Note that the ANC will decrease about 50% per day after the CSF is discontinued if the marrow has not recovered (i.e., if the CSF is discontinued before the ANC nadir is reached).
   12. Avoid the concomitant use of CSF in patients receiving chemotherapy and radiation therapy; the potential exists for worsening myelosuppression.

F. See the American Society of Clinical Oncology guidelines for the following indications: increasing chemotherapy dosage intensity, using as adjuncts to progenitor cell transplantation, administering to patients with myeloid malignancies, and using in pediatric populations.

G. American Society of Clinical Oncology Guidelines for Secondary CSF Administration (secondary prophylaxis)
   1. If chemotherapy administration has been delayed or the dosage reduced because of prolonged neutropenia, then CSF use can be considered for subsequent chemotherapy cycles; administering CSF in this setting is considered secondary prophylaxis.
   2. Dosage reduction of chemotherapy should be considered the first option (i.e., instead of a CSF) after an episode of neutropenia in patients being treated with the intent to palliate (i.e., not a curative intent).

H. Use of CSFs for Treatment of Established Neutropenia
   1. Administering CSFs in patients who are neutropenic but not febrile is not recommended.
   2. Administering CSFs in patients who are neutropenic and febrile may be considered in the presence of risk factors for complications (e.g., sepsis syndrome, age older than 65, ANC less than 100 cells/mm^3, neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection or other clinically documented infections, hospitalization at time of fever, prior episode of febrile neutropenia); CSFs may be used in addition to antibiotics to treat neutropenia in patients with these risk factors.
   3. Pegfilgrastim is not approved for the treatment of established neutropenia.

Patient Case

Questions 5 and 6 pertain to the following case.

A 50-year-old woman is receiving adjuvant chemotherapy for stage II breast cancer. She received her third cycle of AC (doxorubicin and cyclophosphamide) 10 days ago. Her CBC today includes WBC 600 cells/mm^3, segmented neutrophils 60%, band neutrophils 10%, monocytes 12%, basophils 8%, and eosinophils 10%. She is afebrile.

5. Which best represents this patient's ANC?
   A. 600 cells/mm^3.
   B. 360 cells/mm^3.
   C. 240 cells/mm^3.
   D. 420 cells/mm^3.

6. Given this ANC, which statement is most appropriate?
   A. The patient should be initiated on a CSF.
   B. The patient should begin prophylactic treatment with either a quinolone antibiotic or trimethoprim/sulfamethoxazole.
   C. The patient, who is neutropenic, should be monitored closely for signs and symptoms of infection.
   D. Decrease the dosages of AC with the next cycle of treatment.

V. THROMBOCYTOPENIA

A. Megakaryocytes (platelets) = a normal range of 140,000–440,000 cells/mm^3 with a circulating life span of 5–10 days.

B. Thrombocytopenia is defined as a platelet count less than 100,000 cells/mm^3; however, the risk of bleeding is not substantially elevated until the platelet count is 20,000 cells/mm^3 or less. Practices for platelet transfusion vary widely from institution to institution. Many institutions do not transfuse platelets until the patient becomes symptomatic (ecchymosis, petechiae, hemoptysis, or hematemesis). Other institutions transfuse when the platelet count is 10,000 cells/mm^3 or less, even in the absence of bleeding.

C. Caution should be used in patients receiving antiplatelet therapy. Monitor closely and consider interventions as clinically needed (i.e., holding low-molecular-weight heparin product if platelet count is less than 50,000 cells/mm^3).

VI. ANEMIA AND FATIGUE

A. Overview of Anemia
   1. Occurs in 3.4 million Americans each year and most common in women, African Americans, and older adults
   2. Defined as hemoglobin (Hgb) less than 13 g/dL in men or 12 g/dL in women
   3. Anemia defined as a reduction of RBC mass, number of RBCs, and Hgb concentration of RBCs
   4. Caused by a deficiency, impaired bone marrow function, and peripheral causes.
   5. Signs and symptoms of anemia include weakness and fatigue, irritability, tachycardia and palpitations, shortness of breath, chest pain, pale appearance, dizziness, decreased mental acuity, ecchymoses, blood in urine or stool, and hematomas.
   6. There are several types of anemia, including microcytic (iron deficiency anemia), macrocytic/megaloblastic anemia (vitamin B_{12} deficiency, folic acid deficiency), anemia of chronic disease (including chemotherapy-induced anemia), anemia of critical illness, hemolytic anemias, and drug-induced anemias.
   7. Hematologic laboratory values:

Table 5. Hematologic Laboratory Values

Test	Reference Range	Definition
Hgb	M 13.5–17.5 g/dL F 12–16 g/dL	Hgb per volume of whole blood
Hct	M 41–53% F 36%–46%	Percentage of total blood volume composed of RBCs (3 - Hgb)
MCV	80-96 fL	Average volume of RBCs (Hct/RBC)
MCHC	31%–37%	Weight of Hgb per volume (Hgb/Hct)
MCH	26-34pg	Percentage volume of Hgb in RBC (Hgb/RBC)
RBC	4.5-5.9 million/m^3	RBCs per unit blood
Reticulocyte count	0.5%-1.5%	Immature RBCs
RDW	11%-16%	RBC distribution width
EPO	0-19 mU/mL	Endogenous erythropoietin
Serum iron	M 50-160 mcg/dL F 12-150 mcg/dL	Concentration of iron bound to transferrin Transferrin is a glycoprotein that binds and transports iron in the blood to various tissues throughout the body
TIBC	250-400 mcg/dL	Iron binding capacity of transferrin
Ferritin	M 15-200 ng/mL F 12-150 ng/mL	Stored iron concentration
Folate	1.8-1.6 ng/mL	Serum folic acid
Vitamin B12	100-900 pg/mL	Serum vitamin B_{12}
Transferrin saturation	>30%	Serum iron divided by TIBC

EPO = erythropoietin; F = female; Hct = hematocrit; Hgb = hemoglobin; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cells; RDW = RBC distribution width; TIBC = iron binding capacity of transferrin.

B. Microcytic Anemia
   1. Iron deficiency is the most common nutritional deficiency, with laboratory values reflecting a decreased RBC, Hgb/Hct, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), iron, ferritin, and transferrin. Total iron binding capacity (TIBC) and RBC distribution width (RDW) are increased.
   2. Treatment includes oral iron supplementation: 200 mg elemental iron divided twice daily or three times daily for 3–6 months.
   3. Available oral iron products (multiple branded agents):

Table 6. Available Oral Iron Products (multiple branded agents)

Product	% Elemental	Elemental Iron (mg)
Ferrous sulfate 325-mg tablet	20	65
Ferrous gluconate 325-mg tablet	12	39
Ferrous fumarate 100-mg tablet	33	33
Polysaccharide iron complex 150-mg capsule	100	150
Carbonyl iron 50 mg caplet	100	50

   4. Iron adverse effects include constipation and nausea or vomiting.
   5. Iron products should be taken with food to avoid gastrointestinal discomfort (but absorption will be decreased). Vitamin C may increase the absorption of iron and is often used to increase the efficacy of iron products. Iron therapy may cause dark stools.
   6. Parental iron products:

Table 7. Parental Iron Products

	Iron Dextran	Sodium Ferric Gluconate	Iron Sucrose	Ferumoxytol	Ferric Carboxymaltose
Elemental iron	50 mg/mL	62.5 mg/5 mL	20 mg/mL	30 mg/mL	50 mg/mL
Preservative	None	Benzyl alcohol 9 mg/5 mL 20%	None	None	None
Indication	IDA where PO not an option	IDA in patients on chronic HD receiving EPO	IDA in patients on chronic HD receiving EPO	IDA with CKD	IDA with non–dialysis-dependent CKD
Warning	Boxed warning: anaphylactic type reactions	Hypersensitivity reactions	Boxed warning: anaphylactic type reactions	Hypersensitivity reactions	Hypersensitivity reactions
IM injection	Yes	No	Yes	No	No
Usual dosage	100 mg IV push (no faster than 50 mg/min)	125 mg diluted in 100 ml NS over 60 min (IV injection at 12.5 mg/min)	100 mg at 1 mL undiluted solution/ min into dialysis line	510 mg IV injection repeated 3–8 days later	750 mg IV injection repeated 7 days later
Test dose	Yes	No	No	No	No
Common adverse events	Pain, stinging at injection site, local discoloration at injection site, hypotension, flushing, chills, fever, myalgia, anaphylaxis	Cramps, nausea or vomiting, flushing, hypotension, rash, pruritus	Leg cramps and hypotension	Diarrhea, constipation, nausea, dizziness, hypotension, peripheral edema	Hypophosphatemia, dizziness, nausea

CKD = chronic kidney disease; EPO = erythropoietin; HD = hemodialysis; IDA = iron deficiency anemia; IM = intramuscular; IV = intravenous; NS = normal saline; PO = by mouth.

C. Macrocytic Anemia
   1. Vitamin B_{12} and folate deficiency are the most common causes of macrocytic anemia. Causes of B_{12} deficiency include inadequate intake, malabsorption, and inadequate utilization. Folate deficiency is caused by inadequate intake, decreased absorption, hyperutilization, and inadequate utilization.
   2. In B_{12} deficiency RBC, Hgb and Hct, and serum B_{12} are decreased, with an increase in MCV, MCH, methylmalonic acid, and homocysteine. Hypersegmented polymorphonuclear leukocytes may also be present on the peripheral smear.
   3. In folate deficiency, RBC, Hgb and Hct, and serum folic acid are decreased, with an increase in MCV and MCH. B_{12} will be normal (will need to rule out this deficiency).
   4. In B_{12} deficiency, patients may experience neurological changes, glossitis, weakness, loss of appetite, and possibly thrombocytopenia, leucopenia, and pancytopenia. Folate deficiency also presents with glossitis and other central nervous system symptoms including weakness, forgetfulness, headache, syncope, and loss of appetite.
   5. Treatment options for vitamin B_{12} deficiency include oral replacement daily or intramuscular replacement weekly for 1 month, then monthly.
   6. Folate deficiency anemia should be treated with 1 mg of folate daily for 4 months. Pregnant women should take supplements to prevent neural tube defects in the fetus.

D. Anemia of Chronic Disease (Specifically Chemotherapy-Induced Anemia): Causes of Anemia and Fatigue in Adult Patients with Cancer
   1. Unmanaged pain or other symptoms can increase fatigue.
   2. Decreased RBC production because of anticancer therapy, either radiation or chemotherapy
   3. Decreased or inappropriate endogenous erythropoietin production or decreased responsiveness to endogenous erythropoietin
   4. Decreased body stores of vitamin B_{12}, iron, or folic acid
   5. Increased destruction of RBCs
   6. Blood loss
   7. Although anemia can certainly contribute to or worsen fatigue, there are probably other (perhaps many) mechanisms of fatigue (e.g., cytokines) that are independent of Hgb concentration.

E. Principles of Anemia and Fatigue
   1. Fatigue is estimated to affect 60%–80% of all patients with cancer.
   2. Fatigue may be caused by the disease or treatment.
   3. Fatigue can be assessed with a numeric rating scale, 0 = no fatigue and 10 = worst fatigue imaginable, or with any of several questionnaires (e.g., FACT-An).
   4. Drugs used in the treatment of anemia and fatigue
      a. Epoetin and darbepoetin alfa (erythropoiesis-stimulating agents [ESAs]) are approved for treating chemotherapy-induced anemia, the end point of treatment being a decreased need for transfusion. Darbepoetin has additional carboxy chains, resulting in a longer half-life compared with epoetin.
      b. In May 2018, the FDA approved the first biosimilar for the treatment of anemia, epoetin alfa-epbx, for all indications of the originator product. This biosimilar has been studied in patients with chronic kidney disease, but data are limited in patients with cancer. However, a related biosimilar, epoetin zeta, has been approved for use as a biosimilar in Europe since 2007.
      c. Reports of a detrimental effect of ESAs (e.g., increased deaths, reduced chemotherapy outcomes) have led to changes in practice guidelines and reimbursement for these agents. Hgb targets are lower than they were previously, and Hgb is carefully monitored. According to the most recent guidelines, ESAs are initiated once a patient's Hgb drops below 10 g/dL.

d. It is important to distinguish between the use of these agents for chemotherapy-associated anemia and cancer-associated anemia. The latter is not an approved use. These agents should be used only in the noncurative setting.
e. Adverse events: Hypertension and seizures, venous thromboembolism, and pure red cell aplasia (rare)
f. The use of these agents requires baseline and follow-up monitoring to determine whether agents need titration or discontinuation.

5. Transfusions are an option if patients are symptomatic. Transfusion goal is to maintain Hgb at 8–10 g/dL. When considering RBC transfusion, see the AABB 2016 clinical practice guidelines.

F. Dosing of Erythropoiesis-Stimulating Agents

Table 8. Dosing of Erythropoiesis-Stimulating Agents

Agent	Starting Dosage	Dosage Increase	Dosing Parameters
Epoetin alfa or epoetin alfa-epbx (Procrit, Epogen, Retacrit [biosimilar])	150 units/kg subcutaneously 3 times/wk 40,000 units subcutaneously weekly	300 units/kg subcutaneously 3 times/wk 60,000 units subcutaneously weekly	Hgb must be < 10 to initiate and continue therapy Evaluate after 4 wk and increase dosage if rise is < 1 g/dL Decrease by ~25% if rapid rise in Hgb Discontinue therapy if no response after 8 wk
Darbepoetin (Aranesp)	2.25 mcg/kg subcutaneously weekly 500 mcg every 3 wk	4.5 mcg/kg subcutaneously weekly Not applicable	Hgb must be < 10 to initiate and continue therapy Evaluate after 6 wk and increase dosage if rise is < 1 g/dL Decrease by ~40% if rapid rise in Hgb Discontinue therapy if no response after 8 wk

G. REMS for ESAs
1. Historically the FDA required these agents to be prescribed and monitored under a risk management program to ensure their safety.
2. In 2017, the FDA determined that the ESA REMS, which was limited to the use of erythropoietin (Procrit, Epogen) and darbepoetin (Aranesp) to treat patients with anemia caused by chemotherapy, is no longer required.
3. Although the ESA REMS may no longer be required, clinicians should keep these risks in mind and continue to discuss the risk-benefit of using ESAs with each patient before initiating therapy.

Patient Case

7. A 45-year-old woman is beginning her third cycle of chemotherapy for the adjuvant treatment of breast cancer. At diagnosis, her Hgb was 10 g/dL; however, today, it is less than 10 g/dL. The patient has fatigue that is interfering with her activities of daily living. Which is the most appropriate treatment option?

A. Treatment with epoetin should be considered.
B. Treatment with darbepoetin should be considered when Hgb decreases to less than 9 g/dL.
C. The patient is being treated in the curative setting and therefore is not eligible to receive an ESA.
D. The patient should not receive RBC transfusions because she is symptomatic.

VII. CHEMOPROTECTANTS

A. Properties of an Ideal Protectant Drug for Chemotherapy- and Radiation-Induced Toxicities
   1. Easy to administer
   2. No adverse events
   3. Prevents all toxicities, including non–life-threatening (e.g., alopecia) toxicities, irreversible morbidities (e.g., neuropathies, ototoxicity), and mortality (e.g., severe myelosuppression, cardiotoxicity)
   4. Does not interfere with the efficacy of the cancer treatment
   5. To date, no such drug has been identified.

B. Dexrazoxane
   1. The anthracyclines (daunorubicin, doxorubicin, idarubicin, and epirubicin) and anthracenedione (i.e., mitoxantrone) can cause cardiomyopathy that is related to the total lifetime cumulative dosage.
   2. Dexrazoxane acts as an intracellular chelating agent; iron chelation leads to a decrease in anthracycline-induced free radical damage.
      a. Dexrazoxane may be considered for patients who have received doxorubicin 300 mg/m^2 or more and who may benefit from continued doxorubicin, considering the patient's risk of cardiotoxicity with continued doxorubicin use.
      b. Dexrazoxane is dosed in relation to doxorubicin at a ratio of 10:1 dexrazoxane to doxorubicin dose.
      c. Dexrazoxane may increase the hematologic toxicity of chemotherapy at high doses (greater than 750 mg).
      d. An early study suggested that dexrazoxane decreases the response rate to chemotherapy. More recent data suggest this is not the case, but dexrazoxane is still not indicated for patients with early (curable) breast cancer.
   3. Dexrazoxane is also approved for use as an antidote for the extravasation of anthracycline chemotherapy.

C. Amifostine
   1. Amifostine is used to prevent nephrotoxicity from cisplatin.
   2. It is also used to decrease the incidence of both acute and late xerostomia in patients with head and neck cancer who are undergoing fractionated radiation therapy.
   3. Adverse events associated with amifostine include sneezing, allergic reactions, warm or flushed feeling, metallic taste in mouth during infusion, nausea and vomiting, and hypotension. The latter two are the most clinically significant toxicities. Prevention of hypotension includes withholding antihypertensive medications, using hydration, and close blood pressure monitoring. Because of the problems with nausea and vomiting (30%–60%) and the incidence of hypotension, this agent is not often used in clinical practice.

D. Mesna (sodium-2-mercaptoethane sulfonate)
   1. The metabolite acrolein is produced from metabolism of both cyclophosphamide and ifosfamide, and it has been implicated in sterile hemorrhagic cystitis.
   2. Mesna inactivates acrolein by binding to the urotoxic metabolite and preventing its interaction with host cells in the bladder.
   3. Mesna is always used with ifosfamide and may be used with cyclophosphamide (in dosages of 1500 mg/m^2 or greater), although this is not a label indication.
   4. Mesna may be given intravenously or orally and is usually 60%-100% of the ifosfamide dose. The oral dose is twice the parenteral dose. Several dosing schedules may be used. With any schedule, mesna must begin concurrently with or before ifosfamide or cyclophosphamide and end after ifosfamide or cyclophosphamide because of its short half-life (i.e., mesna must be present in the bladder when acrolein is present in the bladder).

E. Leucovorin
   1. Leucovorin rescue may be used after methotrexate doses greater than 100 mg/m2; in general, methotrexate doses greater than 500 mg/m2 require leucovorin rescue.
   2. Factors that increase the likelihood of methotrexate toxicity include renal dysfunction (causing delayed elimination), third-space fluid (e.g., pleural effusion, ascites), and administration of other drugs that may delay methotrexate (pump inhibitors). Toxic reactions include mucous membrane toxicity (e.g., oral mucositis), renal and hepatic toxicity, central nervous system toxicity, and myelosuppression.
   3. The dosage of leucovorin depends on the methotrexate dosage or concentration and the time since completing methotrexate. Methotrexate concentrations are usually obtained 24–48 hours after intermediate-or high-dose methotrexate, and leucovorin is continued until the methotrexate concentration decreases to less than 0.1 mM (less than $1 \times 10\text{-}7$ M). This regimen is typically protocol driven.
   4. In contrast with its use with methotrexate, leucovorin is given in combination with fluorouracil in colorectal cancer to improve activity, not to rescue normal cells

F. Glucarpidase
   1. Glucarpidase, a carboxypeptidase enzyme, is now approved and indicated for treating toxic methotrexate concentrations (greater than 1 micromole/L) in patients with delayed methotrexate clearance because of renal dysfunction.
   2. Administered as a single intravenous dose of 50 units/kg.
   3. Continue leucovorin until the methotrexate concentration has been maintained below the leucovorin treatment threshold for at least 3 days. However, caution must be used with administering leucovorin in conjunction with glucarpidase.
   4. Leucovorin should not be administered within 2 hours before or after a dose of glucarpidase because glucarpidase can decrease leucovorin concentrations. Both are used to prevent methotrexate toxicities, so proper timing of administration is key.

Patient Cases

8. A 38-year-old woman has a history of Hodgkin lymphoma. Two years ago, she completed six cycles of ABVD chemotherapy (i.e., doxorubicin, bleomycin, vinblastine, and dacarbazine). Each cycle included doxorubicin 50 mg/m^2. Recently, she was given a diagnosis of stage IV breast cancer. She will be initiated on doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 for four cycles. Which statement is most applicable?
   A. The patient has not reached the appropriate cumulative dosage of doxorubicin to consider dexrazoxane.
   B. The patient has reached the appropriate cumulative dosage of doxorubicin to consider dexrazoxane
   C. The patient should not receive any more doxorubicin because she is at an elevated risk of cardiotoxicity.
   D. The patient should not receive dexrazoxane because of the possibility of increased myelosuppression.

9. Which is the best sequence for administering mesna and ifosfamide?
   A. Mesna before ifosfamide and then at 4 and 8 hours after ifosfamide.
   B. Ifosfamide before mesna and then at 4 and 8 hours after mesna.
   C. Mesna and ifosfamide beginning and ending at the same time.
   D. Mesna on day 1 and ifosfamide on days 2–5.

VIII. ONCOLOGIC EMERGENCIES

A. Hypercalcemia
   1. The most common tumors associated with hypercalcemia are lung (metastatic non–small cell lung cancer more than small cell lung cancer), breast, multiple myeloma, head and neck, renal cell, and non-Hodgkin lymphoma.
   2. Cancer-associated hypercalcemia results from increased bone resorption with calcium release into the extracellular fluid; in addition, renal clearance of calcium is decreased.
      a. Some tumors cause direct bone destruction, resulting in osteolytic hypercalcemia.
      b. Other tumors release parathyroid hormone–related protein (i.e., humoral hypercalcemia).
      c. Immobile patients are also at an elevated risk of hypercalcemia because of increased resorption of calcium.
      d. Medications (e.g., hormonal therapy, thiazide diuretics) may precipitate or exacerbate hypercalcemia.
      e. Corrected Ca (mg/dL) = (4 – plasma albumin in g/dL) × 0.8 + serum calcium.
      f. Symptoms of hypercalcemia: Lethargy, confusion, anorexia, nausea, constipation, polyuria, and polydipsia
   3. Management of hypercalcemia
      a. Mild hypercalcemia (corrected calcium less than 12 mg/dL) may not warrant aggressive treatment. Hydration with normal saline followed by observation is an option in asymptomatic patients with chemotherapy-sensitive tumors (e.g., lymphoma, breast cancer).
      b. Moderate hypercalcemia (corrected calcium 12–14 mg/dL) requires basic treatment of clinical symptoms with aggressive hydration.
      c. Severe hypercalcemia (corrected calcium greater than 14 mg/dL; symptomatic) requires aggressive inpatient treatment.
         i. Hydration with normal saline about 3–6 L in 24 hours
         ii. Loop diuretics may be administered after volume status has been corrected or to prevent fluid overload during hydration.
         iii. Thiazide diuretics are contraindicated in hypercalcemia because of the increase in renal tubular calcium absorption.
         iv. Bisphosphonates bind to hydroxyapatite in calcified bone, which prevents dissolution by phosphatases and inhibits both normal and abnormal bone resorption. The onset of action is 3–4 days.
         v. Calcitonin (intramuscular formulation) inhibits the effects of parathyroid hormone and has a rapid-onset (though short-lived) hypocalcemic effect. May cause tachyphylaxis
         vi. Steroids may be used to lower calcium in patients with steroid-responsive tumors (lymphoma and myeloma).
         vii. Phosphate is reserved for patients who are both hypophosphatemic and hypercalcemic. Phosphate is seldom used because of the possibility of calcium and phosphate precipitation in soft tissue.
         viii. Dialysis may be needed in patients with hypercalcemia and renal failure.

B. Spinal Cord Compression
   1. Signs and symptoms include back pain, weakness, paresthesias, and loss of bowel and bladder function.
   2. Treatment consists of dexamethasone and radiation therapy or surgery.

C. Tumor Lysis Syndrome
   1. Occurs secondary to the rapid cell death that follows the administration of chemotherapy in patients with leukemia or lymphoma or in patients with high tumor burdens from other diseases that are also highly chemosensitive. Tumor lysis syndrome (TLS) can occur spontaneously in hematologic malignancies, without being triggered by the administration of chemotherapy (i.e., some patients present in tumor lysis).
   2. Manifestations include hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia. Uric acid and calcium/phosphorus may precipitate in the kidney and can lead to renal failure.
   3. The primary management strategy is prevention with parenteral hydration (with normal saline) and allopurinol.
   4. Rasburicase is a recombinant urate oxidase that converts uric acid into allantoin, which is 5–10 times more soluble in urine than uric acid. Rasburicase should be considered for patients at high risk of developing TLS, such as those with a serum uric acid concentration greater than 8 mg/dL, a large tumor burden, preexisting renal dysfunction, or an inability to take allopurinol. The drug is expensive, and currently it is not recommended for prophylaxis in all patients but may be used together with hydration for treatment of TLS. The approved dosage is 0.2 mg/kg intravenously for five doses. There is now increasing evidence for the use of an off-label, low, fixed, single dose of rasburicase for chemotherapy-induced hyperuricemia in adults. The FDA indication is management of uric acid concentrations. Rasburicase causes enzymatic degradation of the uric acid in blood, plasma, and serum samples, potentially resulting in spuriously low plasma uric acid assay readings. Blood must be collected in pre-chilled tubes containing heparin anticoagulant; immediately immerse plasma samples for uric acid measurement in an ice water bath.

IX. MISCELLANEOUS ANTINEOPLASTIC PHARMACOTHERAPY

A. Extravasation Injuries
   1. A vesicant is an agent that, on extravasation, can cause tissue necrosis. Vesicant antineoplastic drugs include doxorubicin, daunorubicin, epirubicin, mechlorethamine, mitomycin, vincristine, vinblastine, vinorelbine, and streptozocin.
   2. Anthracyclines cause the most severe tissue damage on extravasation.
   3. The literature generally recommends administering vesicants by parenteral injection rather than infusion, but some exceptions exist.
      a. Some institutional policies require infusions for every drug or approved protocols.
      b. Vincristine has been incorrectly administered by intrathecal injection, with fatal consequences. Dilution of vincristine for administration as a short parenteral infusion has been recommended to prevent this error from occurring.
      c. Paclitaxel is administered as an infusion (1, 3, or 24 hours, depending on the protocol).
   4. Management of extravasation
      a. Cold for doxorubicin, daunorubicin, and epirubicin
      b. Heat for vincristine, vinblastine, and vinorelbine
      c. Sodium thiosulfate for mechlorethamine
      d. Topical dimethyl sulfoxide has been recommended for anthracyclines. Its use is not as well established as that of the antidotes given earlier. Hyaluronidase is recommended for vinca alkaloids, but hyaluronidase is of limited availability. Antidotes for mitomycin, streptozocin, paclitaxel, and oxaliplatin are not well documented in the literature.
      e. Dexrazoxane (Totect) for doxorubicin, daunorubicin, idarubicin, and epirubicin. Cold compress should be removed 15 minutes before dexrazoxane treatment.

f. Many institutions do not allow the administration of vesicants through a peripheral vein but instead require that vesicants be administered through a central line with a venous access device. Although administering vesicants through a central line minimizes the likelihood of an extravasation injury, extravasation may still occur. Management of extravasation is intended for suspected or actual extravasation from a peripheral or central vein.

B. Management of Diarrhea
   1. Intensive loperamide therapy using dosages higher than recommended is sometimes necessary for irinotecan-induced diarrhea. Atropine is used to prevent cholinergic activity of acute irinotecan-induced diarrhea (given during administration of chemotherapy). There is no maximal dosage of loperamide when used for delayed diarrhea in this setting (greater than 24 hours after irinotecan administration). The recommended dosing regimen of loperamide is 4 mg by mouth, followed by 2 mg every 2 hours until diarrhea free.
   2. Intensive antidiarrhea treatment is also used for other agents (e.g., fluorouracil, epidermal growth factor receptor inhibitors).
   3. Diarrhea/colitis caused by immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab) may require steroid treatment to resolve symptoms.

C. Dosage Adjustment for Organ Dysfunction
   1. Conflicting recommendations for dosage adjustment have been reported. Many drugs have not been studied in patients with organ dysfunction. Consultation of oncology-specific drug information resources may be useful.
   2. Dosage adjustment for renal dysfunction may be considered for methotrexate, carboplatin, cisplatin, etoposide, bleomycin, topotecan, capecitabine, and lenalidomide.
   3. Dosage adjustment for hepatic dysfunction is often based on total bilirubin concentrations and may be considered for anthracyclines, vinca alkaloids, taxanes, methotrexate, and other agents.

D. Immunotherapy-Related Toxicities
   1. There is a dynamic relationship between the immune system and cancer cells. Immune cells can detect genetic and cellular abnormalities located on cancer cells. The immune system has several mechanisms in place to regulate its activation and function.
   2. However, malignant cells can also manipulate the activity of immune cells, allowing cancer cells to evade recognition and destruction by the immune system.
   3. New breakthroughs in immunotherapy have led to many FDA approvals and treatment changes across various malignancies. These treatment developments include immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy.
   4. Some of the most effective immunotherapies to date focus on targeting immune checkpoints that are exploited by cancers to decrease immune activity. Immune checkpoint proteins such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are closely regulated by immune cells to modulate T-cell activity. Cancer cells can disrupt various immune mechanisms, including immune checkpoints, to evade recognition by the immune system.
   5. CTLA-4 and PD-1/PD-L1 inhibitors lead to the reactivation of T-cell populations inhibited by antitumor cells, allowing for immune response against cancer cells.
      a. CTLA-4 is expressed by CD4+ (helper), DC8+ (cytotoxic), and regulatory T cells and functions as an early inhibitory signal during the priming phase. CTLA-4 blockade results in more effector T-cell clones activating and proliferating while reducing the immunosuppressive activity of regulatory T cells.

b. Ipilimumab is a CTLA-4 agent approved for various cancer types as monotherapy and in combination with the PD-1 inhibitor nivolumab.
c. PD-1 receptor is present on various immune cells such as T cells, B cells, and natural killer cells. The ligands of PD-1 (PD-L1 and PD-L2) are expressed in a wide variety of tissue types. PD-L1 is commonly expressed on tumor cells, allowing for possible drug targets. PD-L2 is mainly expressed on hematopoietic cells.
d. Currently available PD-1 inhibitors include cemiplimab, nivolumab, and pembrolizumab.
e. Currently available PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab.

6. Because of the mechanism of immune checkpoint inhibitors, various toxicities may arise from these agents, including immune-related adverse events (irAEs). These toxicities may have an early or late onset and result from various distinct mechanisms that are not yet fully understood. One potential mechanism is T-cell activity directed at antigens present on both tumor cells and healthy tissue, leading to toxicity.
    a. Immune-related toxicities to monitor patients for include the following: diarrhea/colitis, fatigue, hepatitis, hypophysitis, thyroid disorders (hypo/hyperthyroidism), pneumonitis, myocarditis, nephritis, uveitis, and dermatitis.
    b. Patients should be monitored closely for irAEs and counseled on signs and symptoms of these toxicities.
    c. ASCO and NCCN have developed guidelines for the management of immune checkpoint inhibitor toxicities.
    d. General treatment recommendations for moderate to severe (grade 2–4) irAEs involve holding immunotherapy and initiating high-dose corticosteroid treatment with prednisone/methylprednisolone (1–2 mg/kg/day). Severe toxicity management may require inpatient admission and treatment with intravenous corticosteroids.
    e. If patients have irAEs that are refractory to high-dose corticosteroid treatment, other immunosuppressive therapies such as infliximab can be used. Vedolizumab may be considered in patients whose disease is refractory to infliximab and/or for tumor necrosis factor (TNF) alpha blockers such as infliximab are contraindicated. Mycophenolate mofetil should be used for corticosteroid-refractory hepatitis instead of infliximab because of the potential risk of idiosyncratic liver failure with infliximab.
7. CAR T-cell adverse reactions
    a. Cytokine release syndrome (CRS) is a complication related to CAR T-cell administration that occurs in over 50% of patients receiving therapy. CRS results from a massive release of various cytokines (including interleukin [IL]-6, interferon, and TNF). Typical onset is after 2–3 days and typical duration is 7–8 days. Symptoms range from mild to severe and include flu-like symptoms, fever, fatigue, rash, nausea/vomiting, hypoxemia, and hypotension. Treatment involves symptom management, supportive care, and IL-6 inhibitors such as tocilizumab. Corticosteroids can be added to tocilizumab therapy for higher-grade CRS.
    b. Immune effector cell–associated neurotoxicity syndrome (ICANS) is another complication related to CAR T-cell therapy that occurs in around 30%–50% of patients. Typical time to onset is 4–10 days and typical duration is 14–17 days. Symptoms range from mild to severe and include seizure, encephalopathy, and cerebral edema. Management includes supportive care and intravenous fluids, corticosteroids, anti–IL-6 therapy (tocilizumab), and seizure management.

REFERENCES

Antiemetics

1. Gralla RJ, Raftopoulos H. Progress in the control of chemotherapy-induced emesis: new agents and new studies. J Oncol Pract 2009;5:130-3.
2. Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity: state of the art. Support Care Cancer 2010;19:S43-47.
3. Herrstedt J, Dombernowsky P. Anti-emetic therapy in cancer chemotherapy: current status. Basic Clin Pharmacol Toxicol 2007;101:143-50.
4. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. J Clin Oncol 2020. 38(24): 2782-2797
5. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-9.
6. Multinational Association for Supportive Care in Cancer. MASCC/ESMO Antiemetic Guideline 2016. Available at www.mascc.org. Accessed September 12, 2017.
7. Naeim A, Dy SM, Lorenz KA, et al. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol 2008;26:3903-10.
8. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Antiemesis, version 1, 2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed January 4, 2021.
9. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188-95.
10. Navari RM, Nagy CK, Gray SE. Olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2013;21:1655-63.
11. Navari RM, Qin R, Ruddy KJ. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 2016;375:134-42.
12. Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. Int J Clin Oncol 2018;23:382-8.

Pain Management

1. Anderson K, Ismaila N, Flynn PJ, et al. Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2018;36:812-8.
2. Anghelescu DL, Ehrentraut JH, Faughnan LG, et al. Opioid misuse and abuse: risk assessment and management in patients with cancer pain. J Natl Compr Canc Netw 2013;11:1023-31.
3. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: A Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2017;35:2062-81.
4. Foley KM. The treatment of cancer pain. N Engl J Med 1985;313:84-95.
5. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol 2014;32:4149-54.
6. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. JAMA 2017;317:48-58.
7. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol 2020. Online ahead of print. DOI: 10.1200/JCO.20.01399.
8. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Adult Cancer Pain, version 1, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed August 24, 2020.

9. U.S. Department of Health and Human Services (DHHS). Public Health Service Agency for Health Care Policy and Research (AHCPR). Clinical Practice Guideline, No. 9. Management of Cancer Pain. AHCPR Publication 94-0592, March 1994. Washington, DC: DHHS, 1994.
10. U.S. Food and Drug Administration. FDA Approves a Risk Evaluation and Mitigation Strategy (REMS). Available at www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q7. Accessed August 14, 2018.
11. Vadhan-Raj S, von Moos R, Fallowfield LJ, et al. Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid. Ann Oncol 2012;23:3045-51.
12. Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 2011;29:1221-7.

Febrile Neutropenia and CSFs

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. The Infectious Diseases Society of America 2010 guidelines for the use of antimicrobial agents in patients with cancer and neutropenia: salient features and comments. Clin Infect Dis 2011;52:e56-93.
2. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis 2002;34:730-51.
3. Klastersky J, Paesmans M. Risk-adapted strategy for the management of febrile neutropenia in cancer patients. Support Care Cancer 2007;15:477-82.
4. Lyman GH, Allcott K, Garcia J, et al. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Cancer Care 2017;25:2619-29.
5. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors, version 2, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed August 24, 2020.
6. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections, version 2, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed August 24, 2020.
7. Smith TJ, Bohlke K, Lyman GH. 2015 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2015;33:3199-212.

Thrombocytopenia

1. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusions for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1519-38.

Anemia and Fatigue

1. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol 2019;37:1336-51.
2. Losem C, Koenigsmann M, Rudolph C. Biosimilar Retacrit (epoetin zeta) in the treatment of chemotherapy-induced symptomatic anemia in hematology and oncology in Germany (ORHEO) -non-interventional study. Onco Targets Ther 2017;10:1295-305.
3. National Comprehensive Cancer Network (NCCN). Practice Guidelines in Oncology: Hematopoietic Growth Factors, version 2, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf. Accessed November 9, 2020.
4. Tobian AA, Heddle NM, Wiegmann TL, et al. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. Transfusion 2016;56:2627-30.
5. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ 2009;180:E62-71.

Chemoprotectants

1. Bukowsi R. Cytoprotection in the treatment of pediatric cancer: review of current strategies in adults and their application to children. Med Pediatr Oncol 1999;32:124-34.

2. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009;27:127-45.
3. Links M, Lewis C. Chemoprotectants: a review of their clinical pharmacology and therapeutic efficacy. Drugs 1999;57:293-308.
4. Schuchter LM, Hensley ML, Meropol NJ, et al. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2002;20:2895-903.

Oncologic Emergencies

1. Abrahm JL. Management of pain and spinal cord compression in patients with advanced cancer. Ann Intern Med 1999;131:37-46.
2. Brigden ML. Hematologic and oncologic emergencies. Doing the most good in the least time. Postgrad Med 2001;109:143-63.
3. Coiffler B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-78.
4. Krimsky WS, Behrens RJ, Kerkvliet GJ. Oncology emergencies for the internist. Cleve Clin J Med 2002;69:209-22.
5. Nakshima L. Guidelines for the treatment of hypercalcemia associated with malignancy. J Oncol Pharm Pract 1997;3:31-7.
6. Nicolin G. Paediatric update. Emergencies and their management. Eur J Cancer 2002;38:1365-77.
7. Vadhan-Raj S, Fayad LE, Fanale MA, et al. A randomized trial of single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. Ann Oncol 2012;23:1640-5.
8. Yim BT, Sims-McCallum RP, Chong PH. Rasburicase for the treatment and prevention of hyperuricemia. Ann Pharmacother 2003;37:1047-54.

Miscellaneous Antineoplastic Pharmacotherapy

1. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714-68.
2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Management of Immune Checkpoint Inhibitor-Related Toxicities, version 1, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 28, 2020.
3. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society of Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This highly emetogenic regimen is associated with delayed nausea and vomiting. The best choice is a serotonin receptor antagonist with dexamethasone and aprepitant for prophylaxis against nausea and vomiting per NCCN guidelines (Answer A is correct). Prochlorperazine is not effective against a highly emetogenic stimulus (Answer B is not correct). Granisetron and ondansetron are both serotonin receptor antagonists, and no rationale exists for combining them (Answer C is not correct). Lorazepam may be a useful addition, but the combination of ondansetron and metoclopramide is not recommended per NCCN guidelines (Answer D is not correct).

2. Answer: D

Lorazepam is recommended for use in combination with the standard antiemetic regimen based on chemotherapy emetogenicity to prevent anticipatory nausea and vomiting (Answer D is correct). Aprepitant plus palonosetron plus dexamethasone alone has no effects on anticipatory nausea/vomiting, but the combination can be useful for acute and delayed nausea/vomiting (Answer A is not correct). The aprepitant plus prochlorperazine plus dexamethasone regimen does not provide any additional benefit to treat the sensory symptoms (Answer B is not correct). Metoclopramide added to an aprepitant/granisetron regimen would not be appropriate for anticipatory nausea and vomiting (Answer C is not correct).

3. Answer: D

The patient is taking oxycodone/acetaminophen 5 mg/325 mg, which provides 60 mg of oxycodone per day and 3900 mg of acetaminophen. His current drugs should not be increased because of concerns about acetaminophen toxicity. If he were changed to a higher strength of the combination product, acetaminophen toxicity would still be a concern, which eliminates the choices of increasing to oxycodone/acetaminophen the dose to 7.5mg or 10mg (Answer A and B are not correct). Adding sustained-release morphine is a good option and continuing ibuprofen might be helpful for bone pain (Answer D is correct, Answer C is not correct). Oxycodone/acetaminophen, which is short acting, could be continued for breakthrough pain, but he is already receiving high dosages of acetaminophen without good pain relief.

4. Answer: C

Gabapentin might help the neuropathic component (i.e., the shooting pains) of his pain (Answer C is correct). He is already receiving an NSAID, so there is no need to add naproxen (Answer A is not correct). There is no reason to add acetaminophen as it will not provide additional benefit (Answer B). The case does not mention muscle spasms and therefore Baclofen will likely not be effective (Answer D is not correct).

5. Answer: D

To calculate the ANC, multiply the WBC by the segmented neutrophils and the band neutrophils: 600 cells/mm^3 × (0.6 + 0.1) = 420 cells/mm^3 (Answer D is correct). Other options available will not produce the appropriate ANC count due to miscalculation (Answer A, B, and C are not correct)

6. Answer: C

The patient is neutropenic; however, she should not begin a CSF. Her ANC is greater than 100 cells/mm^3, and she has no signs or symptoms of active infection (Answer A is not correct). Prophylactic treatment with antibiotic drugs is not necessary and can increase the risk of resistant organisms (Answer B is not correct). At this time, the patient should be monitored for evidence of infection (e.g., she should be instructed to take her temperature and return to the clinic or emergency department if she has a single oral temperature of 101°F or more or of 100.4°F or more for at least 1 hour or if she develops any signs or symptoms of infection) (Answer C is correct). Because the disease is potentially curable, dosages should not be reduced on the next cycle (Answer D is not correct).

7. Answer: C

Recent literature and subsequent changes in guidelines and Centers for Medicare & Medicaid Services reimbursement suggest that an erythropoiesis-stimulating protein should be considered when Hgb is less than 10 g/dL. However, this patient is being treated potentially for a cure; therefore, she would not be eligible for an ESA (Answer A and B are not correct, Answer C is correct). Transfusions are an option if patients are symptomatic (Answer D is not correct). The transfusion goal is to maintain Hgb at 8–10 g/dL.

8. Answer: B

The patient has received a cumulative dose of 300 mg/m^2 of doxorubicin (50 mg/m^2 × 6 cycles). This is the appropriate cumulative dosage of doxorubicin for dexrazoxane to be considered (Answer A is not correct, Answer B is correct). She is at an elevated risk of cardiotoxicity; however, dexrazoxane protects the heart from this toxicity (Answer C is not correct). Dexrazoxane may increase the myelosuppression from chemotherapy, but that does not represent a contraindication (Answer D is not correct).

9. Answer: A

Several different schedules of ifosfamide and mesna administration exist (e.g., ifosfamide short infusion, followed by intermittent infusions of mesna and continuous infusion of both ifosfamide and mesna). Most schedules recommend the administration of mesna prior to ifosofamide to prevent hemorrhagic cystitis (Answer A is correct, Answer B is not correct). Mesna should always be continued longer than ifosfamide (Answer C and D are not correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

According to the NCCN guidelines, this regimen would likely be considered highly emetogenic. According to these guidelines, an NK1-based regimen with a serotonin-3 antagonist and dexamethasone combination would be recommended (Answer C is correct). However, the patient is likely having some anticipatory nausea/vomiting. Patients who have had poor control of nausea and vomiting on previous cycles of chemotherapy are at an elevated risk of anticipatory emesis. Anxious patients are also at an elevated risk of CINV. Benzodiazepines help decrease anxiety and, by causing anterograde amnesia, may minimize anticipatory symptoms (Answer C is correct). Although it is unclear whether patients who do not respond to one serotonin receptor antagonist will respond to another, a change in regimen is needed (Answer A is not correct). Substituting dolasetron for granisetron would be acceptable, but adding lorazepam is essential (Answer B is not correct). Metoclopramide is another option, but an effective dose might be difficult to administer orally (especially as tablets), and again, adding lorazepam would be preferred to adding aprepitant in this patient(Answer D is not correct).

2. Answer: D

The corrected calcium is 13.6 mg/dL. Corrected calcium concentrations greater than 12 g/dL should be treated with a bisphosphonate (either pamidronate or zoledronic acid) in addition to hydration with normal saline(Answer D is correct). Furosemide may be needed during hydration, but not before hydration because the patient is probably dehydrated (Answer B is not correct). This patient does not need rapid reversal of hypercalcemia; therefore, calcitonin is not needed (Answer A is not correct). Dexamethasone may be used in patients with lymphoma or myeloma, but it has no effect on metastatic non–small cell lung cancer (Answer C is not correct).

3. Answer: C

The patient is at risk of TLS because he has a chemosensitive tumor and a high tumor burden (elevated WBC). Prevention is key in TLS, which includes adequate saline hydration and the use of allopurinol (Answer C is correct). Dextrose 5% is an inappropriate parenteral fluid for hydration because it does not contain saline (Answer A and B are not correct). The value of alkalinization with sodium bicarbonate is somewhat controversial, but alkalinization is not a replacement for allopurinol (Answer D is not correct).

4. Answer: B

This anemia is not attributable to treatment because chemotherapy has not yet begun. Epoetin and darbepoetin are indicated only for noncurative chemotherapy-associated anemia in non-myeloid tumors (answer A is not correct). Chemotherapy should not be delayed, nor should chemotherapy dosages be reduced in the setting of a potentially curable malignancy (Answer C and D are not correct). Therefore, the patient should receive a transfusion of packed RBCs because his hemoglobin is less than 8 g/dL and he is fatigued (Answer B is correct).

5. Answer: B

(55% segmented neutrophils + 5% band neutrophils) $\times$ 500 = 300 cells/mm^3 (Answer B is correct). Other options available will not produce the appropriate ANC count due to miscalculation (Answer A, C and D are not correct)

6. Answer: A

The patient is neutropenic (ANC 300 cells/mm^3). A temperature of 103°F places the febrile neutropenia outside the definition of low-risk febrile neutropenia (Answer B is not correct). Therefore, the patient should be hospitalized for parenteral antibiotics and an infection workup (Answer A is correct). She has none of the appropriate reasons to administer CSFs (i.e., documented pneumonia, hypotension, sepsis syndrome, or fungal infection) (answer C is not correct). Her chemotherapy may need to be delayed, but it should be continued on count recovery (Answer D is not correct). She should receive a CSF with the next cycle of chemotherapy.

7. Answer: B

In this patient, febrile neutropenia developed at the time of the expected neutrophil nadir, 12 days after chemotherapy (Answer B is correct). Marrow recovery would be expected to follow (Answer A is not correct). The percentage of eosinophils may be slightly elevated, but

the absolute count is low (Answer C is not correct). The platelet count is also low, not elevated. Neutrophils are often affected by myelosuppressive chemotherapy to a greater degree than are platelets (Answer D is not correct).

8. Answer: D

Opioids may provide some relief from neuropathic pain, but often, the response to opioids is less than optimal. In general, higher opioid dosages provide greater pain relief; therefore, increasing the dosage of fentanyl and morphine is an option for this patient but will likely not be effective because of the descriptions of neuropathic pain (Answer B is not correct). Adjuvant analgesic drugs, including tricyclic antidepressants and anticonvulsants, are used to help manage neuropathic pain. Gabapentin, with a good adverse event profile, is a reasonable option. However, adjuvant analgesic drugs should not be given to decrease the opioid dosage or discontinue the use of opioid drugs (Answer A is not correct). Adding gabapentin to the current medication profile is the best choice (Answer D is correct). It may be possible to decrease the dosages of opioids later if gabapentin provides adequate pain relief. Diazepam is more effective for muscle spasms than for neuropathic pain, and this option includes decreasing the fentanyl dosage at the same time as the new drug is initiated (Answer C is not correct).

9. Answer: D

Limited-stage small cell lung cancer is potentially curable; therefore, the patient should continue on the planned chemotherapy dosages. The correct dosage of filgrastim is 5 mcg/kg/day subcutaneously, not 250 mcg/m^2 (this is the dose for sargramostim) (Answer A is not correct) . The correct dosage for pegfilgrastim is a single 6-mg injection (Answer C is not correct). Filgrastim should not be given on the same day as chemotherapy (Answer B is not correct, Answer D is correct).

10. Answer: A

Doxorubicin undergoes hepatic clearance (by the biliary tract), and there are recommendations for dosage reduction based on bilirubin (Answer A is correct). There is no reason to reduce the cyclophosphamide dosage (Answer B is not correct). Because only doxorubicin requires reduction, both agents should not be adjusted based on the laboratory values given (Answer D is not correct). Both agents shouldn't be continued at the current dose as doxorubicin must be adjusted in patients with elevated total bilirubin (Answer D is not correct).

11. Answer: A

Large cell lymphoma is faster growing and more chemosensitive than metastatic colorectal cancer (Answer B is not correct). Therefore, patients with large cell lymphoma are more likely to develop hyperuricemia or TLS from rapid cell turnover, both before treatment and after chemotherapy (Answer A is correct). Hypercalcemia is not a common complication of either of these diseases. Some aggressive lymphomas may be associated with hypercalcemia, but pamidronate is used to treat, not prevent, this complication (Answer C and D are not correct).

12. Answer: C

Neither patient should undergo chemotherapy with an ANC of 800 cells/mm^3(Answer A and B are not correct). Both can be treated when neutropenia resolves (probably within 1 week). It is important to keep patient 1 on schedule because his disease is potentially curable; therefore, patient 1 should receive filgrastim after the next chemotherapy treatment to prevent another dose delay (answer C is correct). When patient 2 resumes chemotherapy, his dosages can be decreased to prevent a recurrence of neutropenia (Answer D is not correct).

13. Answer: C

Injury after extravasation of an anthracycline is potentially the most severe. Therefore, when the recommended antidotes for different vesicants conflict (e.g., heat vs. cold), treatment should be directed at the anthracycline (Answer B is not correct). Dexrazoxane is now indicated for doxorubicin extravasation (Answer C is correct). Cold, rather than heat, would also be appropriate (Answer A is not correct). Although vincristine is considered a vesicant, sodium thiosulfate is not the recommended antidote (Answer D is not correct).

14. Answer: A

Immune-related toxicities can occur with immunotherapy such as PD-1/PD-L1 and CTLA-4 inhibitors and are more common with combination therapy such as nivolumab and ipilimumab. This patient has grade 3 colitis related to immune checkpoint inhibitor therapy.

The patient has reported 8 loose stools per day and is dehydrated. Because this is a severe irAE, the patient should be admitted to the hospital for fluid management and high-dose intravenous corticosteroid treatment (Answer A is correct). Because this toxicity is immune related and treatment with steroids is necessary to suppress the immune system in order to reverse the toxicity, loperamide treatment would be inappropriate (Answer B is incorrect). Although discontinuing immunotherapy can be considered for a grade 3 colitis toxicity, it is not required, and the patient may be able to restart therapy once he improves; however, immediate intervention is needed with corticosteroid treatment (Answer C is incorrect). The proper dose of steroid is 1–2 mg/kg/day either orally or intravenously, depending on the severity of the toxicity (Answer D is incorrect).

Gastrointestinal Disorders

Sheila M. Wilhelm, Pharm.D., FCCP, BCPS

Wayne State University
Eugene Applebaum College of Pharmacy and Health Sciences
Detroit, Michigan

Gastrointestinal Disorders

Sheila M. Wilhelm, Pharm.D., FCCP, BCPS

Wayne State University
Eugene Applebaum College of Pharmacy and Health Sciences
Detroit, Michigan

Learning Objectives

1. Review national guideline treatment strategies for the following gastrointestinal (GI) disorders: gastroesophageal reflux disease (GERD); peptic ulcer disease (PUD); ulcerative colitis (UC); Crohn disease (CD); chronic liver disease, including viral hepatitis and cirrhosis; constipation; diarrhea; irritable bowel syndrome (IBS); nausea; vomiting; pancreatitis; and upper GI bleeding, including prevention of stress-related mucosal disease (SRMD).
2. Recommend appropriate pharmacologic and nonpharmacologic interventions given a specific patient with one or more GI disorders.
3. Recognize pertinent information for educating patients and prescribers regarding the appropriate use of pharmacologic agents for various GI disorders.
4. Evaluate and apply evidence related to GI disorders for patient care, including appropriate interpretation or use of study designs and statistical tests.

Abbreviations in This Chapter

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CD	Crohn disease
COX-2	cyclooxygenase-2
CV	cardiovascular
GFR	glomerular filtration rate
GI	gastrointestinal
HAV	hepatitis A virus
HCP	health care provider
HCV	hepatitis C virus
H_2RA	histamine-2 receptor antagonist
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
INR	international normalized ratio
MDF	Maddrey discriminant function
MELD	model for end-stage liver disease
NG	nasogastric
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PPI	proton pump inhibitor
PUD	peptic ulcer disease
SBP	spontaneous bacterial peritonitis
SCr	serum creatinine
TNF	tumor necrosis factor
UBT	urea breath test
UC	ulcerative colitis

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. A 58-year-old African American man presents with a 2-month history of burning epigastric pain and intermittent difficulty swallowing. The pain is not relieved by positional changes or eating, and he has tried calcium carbonate (500 mg) chewable tablets when symptoms occur, resulting in minimal relief. He takes amlodipine 5 mg/day for hypertension and ibuprofen for occasional back pain. Which action is best for this patient?
   A. Initiate famotidine 20 mg/day.
   B. Refer for possible endoscopic evaluation.
   C. Initiate omeprazole 20 mg twice daily.
   D. Change amlodipine to hydrochlorothiazide.

2. A 50-year-old woman is seen in the clinic for severe pain related to the swelling of three of her metacarpophalangeal joints on each hand and swelling of her right wrist. She cannot write or perform her usual household activities. Radiograms of these joints reveal bony decalcifications and erosions. A serum rheumatoid factor is obtained, which is elevated. Her medical history includes type 2 diabetes, hypertension, and dyslipidemia. Her medications include metformin 1000 mg twice daily, glyburide 10 mg/day, metoprolol 100 mg twice daily, aspirin 81 mg/day, and rosuvastatin 5 mg/day. The primary care provider would like to initiate systemic anti-inflammatory therapy for this patient's rheumatoid arthritis with high-dose nonsteroidal anti-inflammatory drug (NSAID) therapy; however, the primary care provider is worried about potential gastrointestinal (GI) toxicity. What is the best regimen for treating this patient's pain while minimizing the risk of GI toxicity?
   A. Celecoxib 400 mg twice daily.
   B. Indomethacin 75 mg/day plus ranitidine 150 mg/day.

C. Naproxen 500 mg twice daily plus omeprazole 20 mg/day.

D. Piroxicam 20 mg/day plus misoprostol 600 mcg three times daily.

3. A 68-year-old Hispanic man is assessed in the emergency department for a 36-hour history of black, tarry stools; dizziness; confusion; and vomiting a substance resembling coffee grounds. He has a medical history of osteoarthritis, hypertension, myocardial infarction (MI) in 2009 and 2011, and seasonal allergies. He has taken naproxen 500 mg twice daily for 4 years, metoprolol 100 mg twice daily, aspirin 325 mg/day, and loratadine 10 mg/day. Nasogastric (NG) aspiration is positive for blood, and subsequent endoscopy reveals a 3-cm antral ulcer with a visible vessel. The vessel is obliterated using an epinephrine solution, and a rapid urease test is negative for *Helicobacter pylori*. Which recommendation is best for this patient?

   A. Intravenous ranitidine 50 mg/hour for 5 days.

   B. Sucralfate 1 g four times daily by NG tube.

   C. Oral lansoprazole 15 mg/day by NG tube.

   D. Pantoprazole 80 mg intravenous bolus, followed by an 8-mg/hour infusion.

4. A 38-year-old woman presents with an 8-week history of new-onset cramping abdominal pain together with 2–4 bloody stools per day. The patient does not have tachycardia or fever. She has a medical history of urinary tract infection and reports an allergy to "sulfa"-containing medications (shortness of breath). Colonoscopy reveals diffuse superficial colonic inflammation consistent with ulcerative colitis (UC). The inflammation is continuous and extends to the hepatic flexure. Which drug therapy is best?

   A. Sulfasalazine extended release tablets 1 g orally three times daily.

   B. Hydrocortisone enema 100 mg every night.

   C. Mercaptopurine 75 mg orally once daily.

   D. Mesalamine (Delzicol) 800 mg orally three times daily.

5. A 45-year-old African American man with a history of alcoholic cirrhosis (Child-Pugh class B) was seen in the clinic for a follow-up. He was recently referred for a screening endoscopy, which revealed several large esophageal varices. He has no history of bleeding; 1 month ago, propranolol 10 mg orally three times daily was initiated. At that time, his vital signs included body temperature 98.7°F (37°C), heart rate 85 beats/minute, respiratory rate 15 breaths/minute, and blood pressure 130/80 mm Hg. At his evaluation today, he seems to be tolerating the propranolol dose and has no new concerns. His vital signs now include body temperature 98.6°F, heart rate 79 beats/minute, respiratory rate 14 breaths/minute, and blood pressure 128/78 mm Hg. What is the best course of action?

   A. Continue current therapy, with a close follow-up in 4 weeks.

   B. Increase propranolol to 20 mg orally three times daily.

   C. Add isosorbide dinitrate 10 mg orally three times daily.

   D. Change propranolol to atenolol 25 mg orally once daily.

6. A new stool antigen test to detect *H. pylori* was tested in 1000 patients with suspected peptic ulcer disease (PUD), and 865 had a positive result. All patients had also undergone a concomitant endoscopy with biopsy and culture as the gold standard comparative test, and 900 had a positive result. Of these 900 patients with confirmed disease, only 850 also had a positive result with the new stool antigen test. From these results, which best represents the sensitivity and specificity of the new stool antigen test?

   A. Sensitivity 82%, specificity 86%.

   B. Sensitivity 85%, specificity 97%.

   C. Sensitivity 94%, specificity 85%.

   D. Sensitivity 96%, specificity 90%.

7. A 50-year-old Asian woman is seeking advice regarding a recent possible exposure to hepatitis A virus (HAV). She saw on the local news report that a chef at a local restaurant where she had eaten about 3 weeks earlier had active HAV. Having heard that HAV could be transmitted through food, she would like to know her options. She has not

previously received the HAV vaccine. Which is the best recommendation for this patient?

A. Initiate HAV vaccine.

B. Administer HAV immune globulin.

C. Continue to observe the patient for symptoms.

D. Initiate HAV vaccine and immune globulin.

8. A 48-year-old woman is admitted to the general medicine floor with abdominal pain, severe nausea and vomiting, and abdominal distension secondary to alcoholic hepatitis. She has a history of alcohol abuse for 20 years and takes no current medications. Her serum creatinine (SCr) is 0.5 mg/dL, aspartate aminotransferase (AST) 250 IU/L, alanine aminotransferase (ALT) 60 IU/L, total bilirubin 10.3 mg/dL, prothrombin time 19 seconds (control 12 seconds), and albumin 2.1 g/L. An abdominal paracentesis shows no evidence of spontaneous bacterial peritonitis (SBP). She reports no known drug allergies. What is the treatment for this patient's alcoholic hepatitis?

A. Naproxen 220 mg orally twice daily.

B. Octreotide 50 mcg/hour intravenously.

C. Prednisolone 40 mg/day.

D. Midodrine 7.5 mg three times daily.

9. A 50-year-old man (weight 80 kg) with a history of intravenous drug abuse and chronic hepatitis C virus (HCV; genotype 3 with compensated cirrhosis and NS5A resistance-associated substitutions present) started taking sofosbuvir 400 mg/velpatasvir 100 mg daily and ribavirin 600 mg orally twice daily 2 weeks ago. He returns to the clinic today with fatigue, scleral icterus, and pallor. There is no clinical evidence of bleeding. Laboratory values reveal the following: hematocrit 31% (baseline 39%), total bilirubin 3.2 mg/dL (indirect 2.7 mg/dL, direct 0.5 mg/dL), AST 150 IU/mL (baseline 300 IU/mL), ALT 180 IU/mL (baseline 400 IU/mL), SCr 0.7 mg/dL, HCV RNA 1×10^6 IU/mL (baseline 2.3×10^6 copies/mL), white blood cell count (WBC) 7.8×10^3 cells/mm^3, and platelet count 160,000/mm^3. What is the most likely cause of this patient's current symptoms?

A. Worsening of his liver disease secondary to inadequate treatment.

B. An adverse effect secondary to treatment with sofosbuvir.

C. Systemic manifestations of chronic HCV disease.

D. An adverse effect secondary to treatment with ribavirin.

10. A 35-year-old man with a history of Crohn disease (CD) is in the clinic today with a chief concern of mucopurulent drainage from an erythematous region on his abdomen. Examination reveals a moderate-size enterocutaneous fistula in the left upper abdominal area. He takes mesalamine (Pentasa) 250 mg in four capsules three times daily and azathioprine 150 mg/day. His physician wants to prescribe infliximab. Which recommendation is best when initiating infliximab therapy?

A. Rule out tuberculosis by purified protein derivative or QuantiFERON-TB test.

B. Administer a test dose before the initial infusion.

C. Admit the patient to the hospital for the administration of all doses.

D. Obtain an echocardiogram to assess cardiac function.

11. A 41-year-old woman (height 65 inches, weight 70 kg) with a history of bipolar disorder and recurrent urinary tract infections is admitted to the general medicine service with severe nausea, vomiting, fever, and back pain. On examination, she has fever, dry mucous membranes, and right-sided costovertebral tenderness. A urinalysis, which reveals many bacteria, is positive for leukocyte esterase. Her SCr is 1.3 mg/dL, and blood urea nitrogen (BUN) is 29 mg/dL. She takes risperidone 6 mg twice daily and sertraline 150 mg/day. She reports an allergy to trimethoprim/sulfamethoxazole that causes a rash. Which drug would be best for treating this patient's nausea?

A. Prochlorperazine 10-mg tablet orally twice daily.

B. Metoclopramide orally disintegrating tablets (ODTs) 5 mg three times daily.

C. Ondansetron 4 mg intravenously three or four times daily.

D. Diphenhydramine 50 mg intravenously three or four times daily.

12. A 75-year-old man (height 58 inches, weight 68 kg) with a history of hypertension, type 2 diabetes, and chronic low back pain is admitted to the hospital for abdominal pain lasting 2 days. He denies fever, chills, or sick contacts. His last bowel movement was 3–4 days ago. On examination, he is afebrile and has moderate left upper and lower quadrant tenderness. An abdominal radiograph reveals large amounts of stool in the colon with no signs of obstruction. He currently takes lisinopril 20 mg/day, verapamil 240 mg once daily, acetaminophen 500 mg four times daily, oxycodone sustained release 20 mg twice daily, and oxycodone/acetaminophen 5/325 mg as needed for pain. His SCr is 1.8 mg/dL (baseline 1.7 mg/dL). Which therapy would best manage this patient's constipation?
    A. Sodium phosphate oral solution.
    B. Bisacodyl suppository.
    C. Methylcellulose tablets.
    D. Methylnaltrexone injection.

13. A 65-year-old man (height 68 inches, weight 79 kg) with a history of hypothyroidism, heart failure, and MI is admitted to the intensive care unit with severe community-acquired pneumonia. Six hours after admission, he develops acute respiratory failure, hypotension, and acute kidney injury from presumed sepsis. Mechanical ventilation is implemented, and an NG tube is placed. He currently takes ramipril 10 mg/day, metoprolol 100 mg twice daily, levothyroxine 125 mcg/day, and aspirin 81 mg/day. His WBC is 25×10^3 cells/mm^3, platelet count is 170,000/mm^3, SCr is 3.8 mg/dL (baseline 1.1 mg/dL), potassium is 4.9 mEq/L, BUN is 65 mg/dL, international normalized ratio (INR) is 1.1, AST is 30 IU/mL, and ALT is 45 IU/mL. Which approach is most appropriate for preventing stress-related mucosal disease (SRMD) in this patient?
    A. Sucralfate 1 g four times daily by NG tube.
    B. Magnesium hydroxide 30 mL four times daily by NG tube.
    C. Cimetidine 8-mg/hour intravenous infusion.
    D. Pantoprazole 40 mg intravenously once daily.

14. A newly available NSAID was designed to reduce the incidence of adverse GI events compared with traditional NSAIDs. A large retrospective cohort study compares the incidence of ulceration and bleeding associated with the use of this new NSAID with the incidence of ibuprofen and naproxen. The results indicate that the new agent is associated with no statistically or clinically significant reduction in ulceration or bleeding with long-term use compared with ibuprofen and naproxen. The investigators of the study argue that the lack of difference in safety is because the drug is being promoted as safer; therefore, most patients receiving it are at a much higher baseline risk of NSAID-induced ulceration and bleeding. If this phenomenon did indeed affect the study results, which potential source of bias would most likely be present?
    A. Recall bias.
    B. Misclassification bias.
    C. Interviewer bias.
    D. Channeling bias.

15. A new enzyme immunoassay for HCV RNA has a reported sensitivity of 95% and a specificity of 92%. If the prevalence of HCV in a cohort of 500 patients is 40%, which value best represents the positive predictive value of this new test?
    A. 75%.
    B. 89%.
    C. 92%.
    D. 96%.

BPS Pharmacotherapy Specialty Examination Content

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain I: Patient-centered pharmacotherapy
   - Tasks 1.1-1.8, 1.11-1.14, 3.2, 4, 5.2
2. Domain II: Drug information and evidence-based medicine
   - Task 2
3. Domain III: System-based standards and population-based pharmacotherapy
   - Tasks 3.1, 6, 7

I. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

A. Definition:
1. GERD is defined by consensus as "symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung." (Am J Gastroenterology 2013;108:308-28). Strength of guideline evidence is rated by the GRADE system (Level of Evidence and Strength).
2. Definition subdivides GERD into the following categories:
   a. Symptoms without erosions on endoscopy (nonerosive reflux disease)
   b. Symptoms with erosions on endoscopy (erosive reflux disease)
3. Symptoms
   a. Typical symptoms: Heartburn (pyrosis), regurgitation, acidic taste in the mouth
   b. Extraesophageal or atypical symptoms: chronic cough, asthma-like symptoms, recurrent sore throat, laryngitis or hoarseness, noncardiac chest pain. Sinusitis, pneumonia, bronchitis, otitis media are less common atypical symptoms. These symptoms require referral for additional testing.
   c. Alarm symptoms: dysphagia, odynophagia, bleeding, weight loss, choking, chest pain, and epigastric mass. These symptoms warrant immediate referral for more invasive testing.
4. Aggravating factors: recumbency (gravity), elevated intra-abdominal pressure, reduced gastric motility (e.g., gastroparesis), decreased lower esophageal sphincter (LES) tone, and direct mucosal irritation.
5. Long-term complications: esophageal erosion, strictures, obstruction, Barrett esophagus (replacement of squamous epithelial cells with columnar epithelial cells within the lower esophagus, resulting in increased risk of esophageal carcinoma), and reduction in quality of life.

B. Diagnosis
1. Symptoms
   a. A presumptive diagnosis of GERD can be made given typical heartburn and regurgitation symptoms. Empiric therapy with a proton pump inhibitor (PPI) is recommended (Strong recommendation/Moderate level of evidence).
   b. Screening for *H. pylori* is not recommended (Strong/Low). *H. pylori* screening is recommended in patients with PUD, a history of a documented peptic ulcer, or gastric mucosa-associated lymphoid tissue (MALT) lymphoma.
   c. Patients with noncardiac chest pain that is suspected to be due to GERD should have a diagnostic evaluation before institution of therapy (Strong/Low).
2. Endoscopy: Upper endoscopy is not necessary in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and in the screening of patients at high risk of complications. Repeated endoscopy is not indicated in patients without Barrett esophagus in the absence of new symptoms (Strong/Moderate).
3. Manometry: Testing to determine esophageal pressure is recommended for preoperative evaluation, but it has no role in the diagnosis of GERD (Strong/Low).
4. Ambulatory pH testing
   a. Ambulatory esophageal reflux monitoring is indicated before considering endoscopic or surgical therapy in patients with nonerosive reflux disease as part of the evaluation of patients who are refractory to PPI therapy and when the diagnosis of GERD is in question (Strong/Low).
   b. Ambulatory reflux monitoring is the only test that can assess reflux symptom association (Strong/Low).
   c. Ambulatory reflux monitoring is not necessary in the presence of short- or long-segment Barrett esophagus to establish a diagnosis of GERD (Strong/Moderate).

C. Treatment Strategies for GERD
   1. Nonpharmacologic interventions and lifestyle modifications are unlikely to control symptoms in most patients. The American College of Gastroenterology (ACG) guidelines cite insufficient evidence to advocate lifestyle modifications for all patients; rather, they advocate use in targeted populations. Thus, the following lifestyle modifications should be implemented only in the patient populations specified.
      a. Dietary modifications if symptoms are associated with certain foods or drinks. Routine global elimination of food triggers is not recommended (Conditional/Low).
         i. Avoid aggravating foods and beverages; some may reduce LES pressure (e.g., alcohol, caffeine, chocolate, citrus juices, garlic, onions, peppermint, spearmint) or cause direct irritation (e.g., spicy foods, tomato juice, coffee).
         ii. Reduce fat intake (high-fat meals slow gastric emptying) and portion size.
         iii. Avoid eating 2–3 hours before bedtime.
         iv. Remain upright for 2 hours after meals.
      b. Weight loss if overweight (body mass index greater than 25 kg/m^2) or recent weight gain (Conditional/Moderate)
      c. Reduce or discontinue nicotine use in patients who use tobacco products (affects LES).; however, evidence is not available in reducing GERD symptoms according to the ACG guidelines.
      d. Elevate head of bed and avoid meals 2–3 hours before bedtime if nocturnal symptoms present (Conditional/Low).
      e. Avoid tight-fitting clothing (decreases intra-abdominal pressure).
      f. Avoid medications that can reduce LES pressure (α-adrenergic antagonists, calcium channel blockers, anticholinergics, theophylline, benzodiazepines, opiates), delay gastric emptying (opiates, tricyclic antidepressants, calcium channel blockers, progesterone), or cause direct irritation (NSAIDs, aspirin, corticosteroids).
   2. Pharmacologic therapies
      a. Initial treatment depends on the severity, frequency, and duration of symptoms.
         i. "Step-down" treatment: starting with maximal therapy, such as therapeutic doses of PPIs, is always appropriate as a first-line strategy in patients with documented esophageal erosion. Advantages: rapid symptom relief, avoidance of over-investigation. Disadvantages: potential overtreatment, higher cost, increased potential for adverse effects.
         ii. "Step-up" treatment: starting with lower-dose over-the-counter (OTC) products for patients with less severe symptoms without evidence of esophageal erosion. Advantages: avoids overtreatment, has lower initial cost. Disadvantages: potential undertreatment (partial symptom relief; may take longer for symptom control; may lead to over-investigation).

b. The ACG treatment guideline recommendation summary follows in Table 1.

Table 1. American College of Gastroenterology (ACG) Treatment Guideline Recommendation

Area	Recommendation (Level/Strength)
Treatment	Treatment duration of at least 4 weeks if no erosive esophagitis present; erosive esophagitis should be treated with an 8-wk course of PPIs; no major differences between PPIs (Strong/High)
	Use maintenance PPIs if return of symptoms or complications (Strong/Moderate)
	Long-term maintenance should be the lowest effective dose, on demand, or intermittent therapy (Conditional/Low)
	Bedtime H_2RAs can be used if morning PPI and nighttime symptoms, but tachyphylaxis develops (Conditional/Low)
	Further testing needed before use of metoclopramide or baclofen (Conditional/Moderate)
Dosing	Traditional PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) should be given 30–60 minutes before meals (Strong/Moderate)
	Newer PPIs (omeprazole-sodium bicarbonate and dexlansoprazole) offer dosing flexibility in relation to meals (Conditional/Moderate)
	Initiate PPIs once daily before a.m. meal (Strong/Moderate)
	Twice-daily PPIs if partial response to once-daily PPIs or nighttime symptoms (Strong/Low)
	Twice daily if partial response to once daily or can switch to another PPI (Conditional/Low)

H_2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor.

Strength of recommendations is based on the GRADE system of Strong/Conditional strength of evidence and High/Moderate/Low levels of evidence.

c. Antacids
   i. Calcium-, aluminum-, and magnesium-based products are available OTC in a variety of formulations (capsules, tablets, chewable tablets, and suspensions).
   ii. Neutralizing acid and raising intragastric pH results in decreased activation of pepsinogen and increased LES pressure; rapid onset of action but short duration, necessitating frequent dosing
   iii. Some products (Gaviscon) also contain the antirefluxant alginic acid, which forms a viscous layer on top of gastric contents to act as a barrier to reflux (variable added efficacy).
   iv. Used as first-line therapy for intermittent (less than twice weekly) symptoms or as breakthrough therapy for those on PPI/histamine-2 receptor antagonist (H_2RA) therapy; not appropriate for healing established esophageal erosions
   v. Adverse reactions: Constipation (aluminum, calcium), diarrhea (magnesium), accumulation of aluminum and magnesium in renal disease with repeated dosing
   vi. Drug interactions: Chelation (e.g., fluoroquinolones, tetracyclines); reduced absorption because of increases in pH (e.g., ketoconazole, itraconazole, iron, atazanavir, delavirdine, indinavir, nelfinavir)

d. H_2RAs
   i. Reversibly inhibit histamine-2 receptors on the parietal cell
   ii. All agents available as prescription and/or OTC products; a variety of formulations available; generics exist for all prescription products. See Table 2 for available H_2RA formulations.
   iii. Recent U.S. Food and Drug Administration (FDA) safety alerts have resulted in recalls of ranitidine products because of the presence of N-nitrosodimethylamine (NDMA), a carcinogen.

Table 2. Histamine-2 Receptor Antagonists

Agent	Oral OTC Formulations	Oral Prescription Formulations	Usual GERD therapeutic dose
Ranitidine (Zantac)	75-mg tablet (Zantac 75) 150-mg tablet (Zantac 150)	150-mg tablets 300-mg tablet 15 mg/mL of syrup 25-mg EFFERdose tablets	150 mg PO BID
Cimetidine (Tagamet)	200-mg tablet (Tagamet-HB)	200-, 300-, 400-, 800-mg tablets 300 mg/5 mL of solution	400 mg PO QID or 800 mg PO BID
Nizatidine (Axid)	Not available	150-mg/300-mg capsules 15 mg/mL of solution	150 mg PO BID
Famotidine (Pepcid) Pepcid Complete	10- and 20-mg tablets (Pepcid AC) 10 mg + 800 mg of calcium carbonate + 165 mg of magnesium hydroxide chewable tablets (Pepcid Complete)	20-mg/40-mg tablets 20-mg/40-mg orally disintegrating tablet 40-mg/5-mL suspension	20 or 40 mg PO BID

BID = twice daily; OTC = over the counter.

   iv. OTC H_2RAs can be used for on-demand therapy for intermittent mild-to-moderate GERD symptoms; preventive dosing before meals or exercise is also possible. Higher prescription doses are often necessary for more severe symptoms or for maintenance dosing. Prolonged use is associated with the development of tolerance and reduced efficacy (tachyphylaxis).
   v. H_2RAs are less effective than PPIs in healing erosive esophagitis.
   vi. Adverse effects: Most are well tolerated. Central nervous system (CNS) effects such as headache, dizziness, fatigue, somnolence, and confusion are the most common. Older adults and patients with reduced renal function are at higher risk. Prolonged cimetidine use is associated rarely with gynecomastia.
   vii. Drug interactions: Can affect the absorption of drugs dependent on lower gastric pH (e.g., ketoconazole, itraconazole, iron, atazanavir, delavirdine, indinavir, nelfinavir) or increases in absorption leading to potential toxicity (e.g., raltegravir, saquinavir). Cimetidine also inhibits cytochrome P450 (CYP) enzymes 1A2, 2C9, 2D6, and 3A4. Warfarin, theophylline, and other agents metabolized by these enzymes can be affected. Cimetidine can also compete with medications and creatinine for tubular secretion in the kidney.

e. Proton pump inhibitors
   i. Irreversibly inhibit the final step in gastric acid secretion; greater degree of acid suppression achieved and typically longer duration of action than H_2RAs
   ii. Most effective agents for short- and long-term management of GERD and for management of erosive disease
   iii. Most costly agents: Several PPIs are available as generic prescription-strength products (e.g., omeprazole, lansoprazole, pantoprazole). Omeprazole, lansoprazole, and esomeprazole available OTC. The OTC products are considered safe and effective for intermittent short-term (2 weeks) use in patients with typical heartburn symptoms. Long-term use of OTC products should be discussed with prescriber to prevent loss of follow-up or to assess for potential over or undertreatment.
   iv. Most effective when taken orally before meals; for divided dosing, give evening dose before evening meal instead of at bedtime. See Table 3 for available PPI products and Table 4 for alternative PPI administration options.

Table 3. Proton Pump Inhibitors

Product	Formulations	Standard dose (High dose)[a]
Esomeprazole (Nexium) (Nexium 24HR OTC)	Delayed-release capsule IV solution Delayed-release oral suspension Delayed-release capsule Delayed-release capsule or tablet	20 mg once daily (40 mg once daily)
Omeprazole (Prilosec) Prilosec OTC Zegerid OTC	Delayed-release capsule Delayed-release tablet (magnesium salt) Immediate-release powder for oral suspension; sodium bicarbonate buffer = 460 mg of Na^+/dose (two 20-mg packets are not equivalent to one 40-mg packet) Zegerid OTC immediate-release capsules with sodium bicarbonate	20 mg once daily (40 mg once daily)
Lansoprazole (Prevacid) (Prevacid 24HR)	Prevacid 24HR delayed-release capsule Delayed-release capsule Delayed-release oral suspension Delayed-release orally disintegrating tablet	30 mg once daily (30 mg twice daily)
Rabeprazole (AcipHex)	Delayed-release enteric-coated tablet (20 mg) Sprinkle capsule (5 mg, 10 mg)	20 mg once daily (20 mg twice daily)
Pantoprazole (Protonix)	Delayed-release tablet (20 mg/40 mg) IV solution (40 mg/vial) Pantoprazole granules 40 mg/packet	40 mg once daily (40 mg twice daily)
Dexlansoprazole (Dexilant)	Delayed-release capsule (30 mg/60 mg)	30 mg once daily (60 mg once daily)
Esomeprazole strontium	Delayed-release capsule (20 mg/40 mg base)	20 mg once daily (40 mg once daily)

[a]High-dose therapy is reserved for patients with inadequate response to standard doses.

IV = intravenous; OTC = over the counter.

Table 4. Alternative administration of PPIs

Product	Alternative Administration Technique
Omeprazole (Prilosec) Esomeprazole (Nexium) Zegerid	Open capsules; mix with applesauce or juice Simplified omeprazole suspension; contents dissolved in bicarbonate (NG/OG) Open esomeprazole capsules and mix with 60 mL of water by NG tube, or dissolve oral suspension in 15 mL of water and administer by NG tube; IV bolus, or continuous infusion Zegerid mix packet with 20 mL water in syringe (NG)
Lansoprazole (Prevacid)	Open capsules; mix with applesauce, ENSURE, cottage cheese, pudding, yogurt, or strained pears, or 60 mL of tomato, orange, or apple juice Open capsules + 40 mL of apple juice (NG/OG) Simplified lansoprazole suspension; contents dissolved in bicarbonate (NG/OG) Do not use oral suspension for NG/OG; mix packet with 30 mL of water and swallow Orally disintegrating tablet by oral syringe: Use 4 mL of water for 15 mg tablet or 10 mL of water for 30 mg tablet Orally disintegrating tablet by NG tube (> 8 French): Same preparation as for oral syringe
Rabeprazole (AcipHex)	Do not crush Empty sprinkle capsule contents into liquid or soft food and administer within 15 min of preparation. Sprinkle capsule should not be swallowed whole or contents chewed or crushed
Pantoprazole (Protonix)	Do not crush IV (bolus or continuous infusion) Pantoprazole suspension (compounded with bicarbonate)
Dexlansoprazole (Dexilant)	Open capsules and sprinkle on applesauce

IV = intravenous; NG = nasogastric; OG = orogastric.

iv. Adverse reactions
   (a) Overall, well tolerated; possible adverse effects include headache, dizziness, nausea, diarrhea, and constipation. Long-term use is not associated with significant increases in endocrine neoplasia or symptomatic vitamin B_{12} deficiency. As an option, the 2013 AGA guidelines list the switching of PPIs in patients having adverse effects (Conditional/Low).
   (b) Summary of major adverse effects of PPIs and prevention and management strategies can be found in Table 5.

Table 5. Summary of Major Adverse Effects of PPIs and Prevention and Management Strategies

Adverse Effect	Prevention and Management
Acute interstitial nephritis (AIN)	Limit the dose and duration of PPIs. Renal function monitoring may not be necessary for short-term use (4–8 weeks) use; consider annual monitoring, dose reduction, and deprescribing in patients with long-term use. AIN may recur with PPI rechallenge
Risk of fracture (hip, wrist, spine)	Concern about fractures should not affect decision to use PPIs, except in patients with other risk factors for hip fracture (Strong/Moderate); patients with osteoporosis can remain on PPIs; limit dose and duration; ensure adequate calcium and vitamin D; BMD screening if at risk of low bone mass; weight-bearing exercise
Hypomagnesemia	Reevaluate need of PPI use; limit dose and duration; consider baseline testing (presence of diuretics, digoxin); supplementation

Table 5. Summary of Major Adverse Effects of PPIs and Prevention and Management Strategies *(continued)*

Adverse Effect	Prevention and Management
Clostridioides difficile–associated diarrhea	Reevaluate need of PPI use; limit dose and duration; evaluate for *C. difficile* if patient receiving PPI has diarrhea that is not improving; have patients report diarrhea
Community-acquired pneumonia	Short-term use may increase risk; long-term risk is not elevated (Conditional/Moderate); assess vaccine status

BMD = bone mineral density; PPI = proton pump inhibitor.

v. Drug interactions
  (a) Inhibition of CYP450: Omeprazole inhibits the metabolism of substrates, such as diazepam, through CYP2C19 inhibition.
    (1) Potential reduced effectiveness of clopidogrel through inhibition of CYP2C19-mediated conversion to active metabolite by omeprazole. Recommendations from the FDA are to avoid omeprazole and to use pantoprazole as an alternative. The 2013 ACG guidelines consider the PPI/clopidogrel interaction not clinically significant (Strong/High).
    (2) Interaction with high-dose intravenous methotrexate. The labeling for both intravenous methotrexate and the PPIs has been updated to include this interaction, which places patients at higher risk of methotrexate toxicity. Proposed mechanisms include reduced methotrexate excretion by PPI inhibition of BCRP (breast cancer resistance protein), an efflux pump that transports methotrexate across membranes, or reduced renal excretion by inhibition of renal H^+/K^+-ATPase. Patients receiving high-dose intravenous methotrexate should avoid PPI use, with a switch to ranitidine if needed. Holding the PPI dose for 2 days before and after methotrexate administration can prevent the interaction.
  (b) Drugs with pH-dependent absorption (e.g., ketoconazole, itraconazole, protease inhibitors)

f. Promotility agents
  i. The 2013 guidelines state that prokinetic therapy or baclofen should not be used in patients with GERD without diagnostic evaluation (Conditional/Moderate).
  ii. Metoclopramide: dopamine antagonist; dosed several times a day; associated with adverse effects such as dizziness, fatigue, drowsiness, extrapyramidal symptoms (EPS), and hyperprolactinemia; 5- and 10-mg ODT formulations are available; used for GERD and diabetic gastroparesis.
  iii. Bethanechol: cholinergic agonist; poorly tolerated because of adverse effects such as diarrhea, blurred vision, and abdominal cramping; may also increase gastric acid production. Used for urinary retention, off-label for GERD

g. Surgical therapy
  i. Surgical therapy (Nissen fundoplication) is a laparoscopic procedure for long-term therapy in patients with GERD (Strong/High).
  ii. Surgical therapy is generally not recommended in patients who do not respond to PPI therapy (Strong/High).
  iii. Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon (Strong/High).
  iv. Patients with obesity contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients (Conditional/Moderate).
  v. Current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy (Strong/Moderate).

D. Management of dyspepsia was recently reviewed by the American College of Gastroenterology and the Canadian Association of Gastroenterology. The recommendations include endoscopy for patients at risk for serious outcomes, testing and eradicating *H. pylori*, and using PPIs, tricyclic antidepressants, prokinetic agents, and psychotherapy to manage symptoms.

Patient Case

1. A 55-year-old man with an 8-month history of GERD symptoms 4–5 days/week has been receiving lansoprazole 15 mg daily by mouth, with the use of magnesium hydroxide for breakthrough symptoms. His symptoms are still present 3–4 days/week and are disruptive to his daily life. He has implemented lifestyle modifications and has been adherent to lansoprazole. His medical history is significant for hypothyroidism. He takes levothyroxine 100 mcg once daily. An endoscopy last week revealed no ulcers or erosions. Which treatment approach is best for this patient?
   A. Add metoclopramide 10 mg four times daily.
   B. Increase lansoprazole to 15 mg twice daily.
   C. Switch to omeprazole 20 mg daily.
   D. Add sucralfate 1000 mg four times daily.

II. PEPTIC ULCER DISEASE

A. Classification of peptic ulcer disease (PUD)
   1. Duodenal ulcer
      a. Common causes: *H. pylori* infection (95%), NSAIDs, low-dose aspirin
      b. Uncommon causes: Zollinger-Ellison syndrome, hypercalcemia, granulomatous diseases, neoplasia, infections (cytomegalovirus, herpes simplex, tuberculosis)
      c. Presentation: epigastric pain, possibly worse at night; often, pain occurs 1–3 hours after a meal and may be relieved by eating. Pain may also be episodic. Associated symptoms can include heartburn, belching, a bloated feeling, nausea, and anorexia.
   2. Gastric ulcer
      a. Common causes: NSAIDs, *H. pylori* infection
      b. Uncommon causes: CD, infections (cytomegalovirus, herpes simplex)
      c. Presentation: epigastric pain, often made worse by eating; associated symptoms may include heartburn, belching, a bloated feeling, nausea, and anorexia
   3. Complications of PUD
      a. Bleeding
      b. Gastric outlet obstruction
      c. Perforation
   4. Patients at risk of NSAID-induced GI toxicity: Risk factors for NSAID-induced GI complications can be found in Table 6.

Table 6. Risk Factors for NSAID-Induced Gastrointestinal Complications

Category	Risk Factors
High risk	History of complicated ulcer Several (> 2) risk factors
Moderate risk (1 or 2 risk factors)	Age > 65 yr High-dose NSAID therapy (e.g., ibuprofen 2400 mg/day, naproxen 1000 mg/day) History of uncomplicated ulcer Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants
Low risk	No risk factors

NSAID = nonsteroidal anti-inflammatory drug.

a. Some NSAIDs such as ibuprofen, diclofenac, and nabumetone are intrinsically less toxic to the GI tract than naproxen, which is considered a moderate risk. Other agents such as piroxicam, indomethacin, and ketorolac are considered high-risk agents.
b. Duration of NSAID use (higher risk in first 3 months). The presence of chronic debilitating disorders, such as rheumatoid arthritis or cardiovascular (CV) disease, could also contribute to the increased GI toxicity of NSAIDs, but these are not generally considered independent risk factors.
c. *H. pylori* infection is thought to confer additive risk of GI toxicity in NSAID users; however, evidence of H. pylori eradication in patients using NSAIDs is not conclusive..

5. Diagnosis
   a. Symptom presentation
   b. Testing for *H. pylori* infection: Practitioners must be willing to treat if test results are positive, because *H. pylori* is a known carcinogen.
      i. Testing is indicated for patients with active ulcer disease, history of PUD, or gastric MALT lymphoma.
      ii. The *H. pylori* test-and-treat strategy is also acceptable for patients with unevaluated dyspepsia without alarm symptoms who are younger than 60 years.
   c. Diagnostic tests for *H. pylori* infection
      i. Noninvasive tests are preferred over invasive tests for ease of use.
         (a) Serologic tests (QuickVue *H. pylori* gII, FlexSure HP): Detect immunoglobulin (Ig) G to *H. pylori* in the serum by enzyme-linked immunosorbent assay (85% sensitive, 79% specific). Cannot distinguish between active infection and past exposure. Because antibodies persist for long periods after eradication, cannot use to test for eradication after treatment.
         (b) Urea breath test (UBT; BreathTek UBT, PYtest) detects the exhalation of radiolabeled CO_2 after the ingestion of ^{13}C- or ^{14}C-radiolabeled urea. *H. pylori* hydrolysis of the radiolabeled urea results in CO_2 production (97% sensitive, 95% specific. It is used to make a diagnosis and to test for eradication. Recent use of antibiotics or PPIs can cause false-negative results in up to 40% of patients. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before UBT testing or wait 4 weeks after treatment has ended before having the UBT performed.
         (c) Stool antigen tests (Premier Platinum HpSA, ImmunoCard STAT! HpSA) are polyclonal or monoclonal antibody tests that detect the presence of *H. pylori* in stool (88%–92% sensitive, 87% specific). They can be used to make a diagnosis and to confirm eradication. Recent use of bismuth, antibiotics, or PPIs can also cause false-negative results. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before stool antigen testing or wait 4 weeks after treatment has ended before having the stool antigen test performed.

ii. Invasive (endoscopic) tests are used less frequently than noninvasive tests.
   (a) Histology: 90%–95% sensitive, 98%–99% specific, subject to sampling error
   (b) Rapid urease tests (*Campylobacter*-like organism [CLO] test, Hp-fast, and PyloriTek) detect the presence of ammonia (NH_3) in a sample generated by *H. pylori* urease activity (80%–95% sensitive, 95%–100% specific). False-negative results can be caused by a partly treated infection, GI bleeding, achlorhydria, or use of PPIs, H_2RAs, or bismuth. Patients should discontinue antisecretory agents for at least 1 week before the test is performed.
   (c) Culture is costly, time-consuming, and technically difficult (100% specific).

B. Treatment of *H. pylori*–associated ulcers
   1. General recommendations, based on the American College of Gastroenterology (ACG) guidelines, are to include an antisecretory agent (preferably a PPI) plus at least two antibiotics (clarithromycin and amoxicillin or metronidazole) in the eradication regimen. Specific treatment regimens are listed in Table 7.
   2. Quadruple therapy with bismuth subsalicylate, metronidazole, tetracycline (or doxycycline in the case of drug shortages), and a PPI is considered an alternative first-line treatment. Pylera, a quadruple based therapy formulated with tetracycline, bismuth subcitrate, and metronidazole in 1 capsule, can be used by patients with aspirin allergy.
   3. Sequential therapy involves administration of a PPI and amoxicillin given for the first 5 days, followed by a PPI, clarithromycin, and tinidazole for an additional 5 days. This therapy requires further validation before widespread use will be accepted.
   4. A bismuth-based quadruple therapy for 14 days or a levofloxacin-based triple therapy for 10 days can be used in patients who have not responded to initial regimens as salvage therapy.
   5. Follow-up testing for eradication should be performed in patients with a history of ulcer complication, MALT lymphoma, early gastric cancer, or recurrence of symptoms.
   6. UBTs or stool antigen tests are preferred for confirming eradication (should wait at least 4 weeks after treatment for both).
   7. Patients should be asked about prior use of antibiotics, and this information should be considered when the treatment regimen is chosen (ACG).

Table 7. Recommended Treatment Regimens for *Helicobacter pylori* Infection

Regimen	Drugs and doses	Notes
Clarithromycin triple	PPI (standard or double dose) BID + amoxicillin 1000 mg BID or metronidazole 500 mg TID + clarithromycin 500 mg BID for 14 days	Avoid if clarithromycin resistance rate is known to be > 15% or in patients with prior macrolide exposure
Bismuth quadruple	PPI (standard dose) BID + Bismuth subsalicylate 300 mg QID or Bismuth subcitrate 120-300 mg QID + metronidazole 250 QID or 500 mg TID-QID + tetracycline 500 mg QID[d] x 10-14 days	Initial treatment choice if clarithromycin resistance rates are high or patient has prior macrolide exposure. Also beneficial to patients with penicillin allergy
Concomitant	PPI (standard dose) BID + clarithromycin 500 mg BID + amoxicillin 1000 mg BID + metronidazole or tinidazole 500 mg BID for 10-14 days	Appears at least as effective as clarithromycin triple therapy, although not validated in North America
Sequential	PPI (standard dose) BID + amoxicillin 1000 mg BID for 5–7 days; then PPI BID + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID for 5–7 days	Efficacy subject to geographic variation of resistance rates; complexity of regimen makes it less desirable as first line therapy

Table 7. Recommended Treatment Regimens for *Helicobacter pylori* Infection *(continued)*

Regimen	Drugs and doses	Notes
Hybrid	PPI (standard dose) BID + amoxicillin 1000 mg BID for 7 days; then PPI BID + amoxicillin 1 g BID + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID for 7 days	Regimen not studied in North America; complexity of regimen makes it less desirable as first line therapy
Levofloxacin triple	PPI (standard dose) BID + levofloxacin 500 mg daily + amoxicillin 1000 mg BID for 10–14 days	Lack of North American data; concerns for high levofloxacin resistance rates. Additional risks associated with fluoroquinolone therapy such as high North American resistance rates and adverse affects should be considered
Levofloxacin sequential	PPI (standard or double dose) BID + amoxicillin 1000 mg BID for 5-7 days; then PPI BID + amoxicillin 1000 mg BID + levofloxacin 500 mg daily + metronidazole or tinidazole 500 mg BID for 5-7 days	Lack of North American data; may be more effective than levofloxacin triple therapy
LOAD	PPI (double dose) daily + levofloxacin 250 mg daily + metronidazole or tinidazole 500 mg BID + doxycycline 100 mg daily	Lack of North American data; may be more effective than levofloxacin triple therapy

BID = twice daily; PPI = proton pump inhibitor; QID = four times daily; TID = three times daily.

C. Primary prevention of NSAID-induced ulcers
   1. Implement risk factor modification.
   2. Test and treat for *H. pylori* infection if the patient is beginning long-term NSAID therapy.
   3. Determine the level of GI-related risk (low, medium, high) using Table 6. See Box 1 for strategies to prevent GI complications in patients receiving NSAIDs based on their CV risk.
   4. Because of the association of increased risk of CV events with NSAID use, the patient's CV risk should be determined as well. The ACG guidelines define those at high CV risk as patients who require low-dose aspirin for the prevention of cardiac events. Naproxen is the only NSAID that does not appear to increase the risk of CV events; therefore, its use is preferred in patients with CV risk factors per the ACG guidelines. However, in 2015, the FDA required that warnings regarding the risk of myocardial infarction and strokes be attached to NSAID products (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory).

Box 1. Preventive Strategies Based on Risk of NSAID-Related GI Complications and CV Risk

If low CV risk and:
Low GI risk[a] → NSAID (lowest dose of least ulcerogenic agent)
Moderate GI risk[b] → NSAID + PPI or misoprostol
High GI risk[c] → COX-2 inhibitor + PPI or misoprostol
If high CV risk (requirement for low-dose aspirin) and:
Low GI risk[a] → Naproxen + PPI or misoprostol
Moderate GI risk[b] → Naproxen + PPI or misoprostol
High GI risk[c] → Avoid NSAIDs or COX-2 inhibitors

[a]No risk factors.

[b]One or two risk factors present (see Table 6).

[c]Positive history of ulcer complication or several (more than two) risk factors or use of steroids and anticoagulants.

COX-2 = cyclooxygenase-2; CV = cardiovascular; NSAID = nonsteroidal anti-inflammatory drug.

5. Misoprostol (Cytotec) should be given at full doses (800 mcg/day in four divided doses); however, this therapy is poorly tolerated because of excessive nausea, vomiting, diarrhea, and abdominal cramping.
6. Concomitant use of antiplatelet agents and NSAIDs
    a. Need for antiplatelet therapy should first be evaluated.
    b. If antiplatelet therapy is deemed necessary, assess for the presence of GI risk factors (see Table 6). Dyspepsia or GERD symptoms are additional risk factors.
    c. Test and treat for *H. pylori* in patients with a history of a nonbleeding ulcer and in those with a history of an ulcer-related complication. Eradicating *H. pylori* before beginning long-term antiplatelet therapy is optimal.
    d. PPIs are the preferred gastroprotective agents for both treatment and prevention of aspirin- and NSAID-associated GI injury.
    e. Gastroprotective therapy should be prescribed for patients with GI risk factors who require the use of any NSAID (including OTC and cyclooxygenase-2 [COX-2] inhibitors) in conjunction with low-dose aspirin.
    f. Gastroprotective therapy should be prescribed for patients with GI risk factors who require low-dose aspirin. Aspirin doses greater than 81 mg/day should not be used in patients with GI risk factors during the long-term phase of aspirin therapy.
    g. PPIs should be prescribed for patients receiving concomitant aspirin and anticoagulant therapy (unfractionated heparin, low-molecular-weight heparin, argatroban, warfarin, direct oral anticoagulants, and fondaparinux).
    h. The target INR range of 2–2.5 should be used in patients for whom warfarin is added to concomitant aspirin and $P2Y_{12}$ inhibitor (e.g., clopidogrel, prasugrel, ticagrelor) therapy. The combination of both aspirin and clopidogrel with warfarin should be used only when benefit outweighs risk.
    i. Clopidogrel is not recommended as a substitute for patients with recurrent ulcer bleeding. Aspirin plus a PPI is superior to clopidogrel for GI bleed risk.
    j. The health care provider (HCP) who decides to discontinue aspirin therapy in patients with short-term bleeding episodes should weigh the risks of subsequent GI or cardiac events.
    k. For patients receiving dual antiplatelet therapy (aspirin plus clopidogrel) who require elective endoscopy (particularly colonoscopy and polypectomy), consider deferring if patient is at high risk of cardiac events. Elective endoscopy should be deferred for 1 year after the placement of drug-eluting stents.

D. Treatment and secondary prevention of NSAID-induced ulcers
   1. Risk factor modification
   2. Discontinue or lower NSAID dose, if possible. Ulcers will heal with appropriate treatment, but healing may take longer with continued NSAID use.
   3. Test for *H. pylori* and treat, if present.
   4. Drug therapy
      a. PPIs: Drugs of choice for healing and secondary prevention of NSAID-induced ulcers. Combination product Vimovo contains esomeprazole with naproxen in the same tablet (375 mg/20 mg or 500 mg/20 mg) but may be expensive.
      b. Misoprostol appears to be as effective as PPIs for healing and secondary prevention; however, it necessitates several doses per day, and it is poorly tolerated because of the high incidence of diarrhea and abdominal pain.
      c. COX-2 inhibitors: Celecoxib was shown to have rates of ulcer recurrence and bleeding comparable to those of a diclofenac plus omeprazole combination. The use of celecoxib may be limited by its association with CV effects. The use of celecoxib is also uncertain in combination with low-dose aspirin for secondary prevention of GI events.
      d. The combination of a COX-2 inhibitor and a PPI is not well studied, but it can be considered in high-risk patients, especially if receiving aspirin plus steroids or warfarin or have a history of a recent complicated GI event and require continued NSAID or aspirin use.
      e. H_2RAs are inferior to misoprostol and PPIs in healing and preventing recurrence.
      f. Clopidogrel is not recommended as a substitute in patients with recurrent ulcer bleeding. Aspirin plus a PPI is superior to clopidogrel for GI bleed risk.
   5. CV safety of COX-2 inhibitors and NSAIDs
      a. The main theory underlying the development of excess thrombotic events with COX-2 inhibitor use is that when COX-2–mediated prostacyclin production is reduced, the prothrombic prostaglandin thromboxane A continues to be produced by COX-1, leading to the development of a prothrombic state.
      b. Celecoxib was not associated with increases in CV events until the Adenoma Prevention with Celecoxib trial for cancer prevention was terminated in 2004. Daily doses of 400 and 800 mg of celecoxib conferred a 2.5- and 3.4-fold higher risk of fatal and nonfatal MI, respectively, which suggests a dose-related response for this toxicity.
      c. The AHA recommends a stepped approach for patients with CV disease or risk factors for ischemic heart disease who require analgesic treatment of musculoskeletal symptoms.
         i. Consider using acetaminophen, aspirin, tramadol, or short-term narcotics first.
         ii. Nonacetylated salicylates (e.g., salsalate, choline magnesium trisalicylate) can be considered next.
         iii. Non–COX-2-selective NSAIDs can be used next, followed by NSAIDs with some COX-2 activity. Use the lowest possible effective dose.
         iv. Celecoxib should be reserved as a last resort. In patients at increased risk of thromboembolic events, coadministration with aspirin and a PPI can be considered.
         v. Routinely monitor blood pressure, renal function, and signs of edema or GI bleeding.
      d. Methods to reduce CV risk, such as tobacco cessation, blood pressure reductions, lipid control, and glucose control, are recommended for NSAID users, but have not been proved to reduce NSAID-associated CV risk. In patients for whom the risk of GI bleeding outweighs the CV risk, lower-risk NSAIDs such as ibuprofen, etodolac, diclofenac, or celecoxib should be used. In patients for whom the CV risk outweighs the risk of GI bleeding, COX-2 inhibitors should be avoided. Limit the dose and therapy duration, if possible.

e. The AHA recommends that ibuprofen be taken at least 30 minutes after or 8 hours before the ingestion of immediate-release low-dose aspirin to prevent the ibuprofen from attenuating the antiplatelet effects of the aspirin.

Patient Cases

2. A 68-year-old woman referred to a gastroenterologist has intermittent upper abdominal pain with anemia and heme-positive stools. She has a history of hypertension and type 2 diabetes with peripheral neuropathy. She reports no known drug allergies and takes metformin 1000 mg twice daily, aspirin 325 mg daily, lisinopril 20 mg daily, and gabapentin 1000 mg three times daily. In addition, she reports using OTC ketoprofen daily for the past 2 months secondary to uncontrolled pain. The results of a colonoscopy are negative, but endoscopy reveals a 1-cm gastric ulcer with an intact clot. A rapid urease test for CLO is negative. Which treatment is best for this patient's ulcer?
   A. Ranitidine 150 mg twice daily for 4 weeks.
   B. Lansoprazole 30 mg twice daily plus amoxicillin 1000 mg twice daily plus clarithromycin 500 mg twice daily for 10 days.
   C. Lansoprazole 30 mg/day for 8 weeks.
   D. Misoprostol 200 mcg twice daily for 8 weeks.

3. A 42-year-old man is in the clinic with the chief concern of sharp epigastric pain for the past 6 weeks. He states that the pain is often worse with eating and that it is present at least 5 days/week. He states that although he initially tried OTC antacids with some relief, the pain returns about 3 hours after each dose. He currently takes no other medications. He reports an allergy to sulfa-containing medications (rash). His practitioner is concerned about a potential peptic ulcer and tests him for *H. pylori* using a UBT, the result of which is positive. Which treatment for *H. pylori* is best?
   A. Amoxicillin 1 g twice daily plus clarithromycin 500 mg twice daily plus omeprazole 20 mg twice daily for 5 days.
   B. Cephalexin 1 g twice daily plus clarithromycin 500 mg twice daily plus omeprazole 20 mg twice daily for 10 days.
   C. Bismuth subsalicylate 525 mg four times daily plus tetracycline 500 mg four times daily plus metronidazole 500 mg three times daily plus omeprazole 20 mg twice daily for 14 days.
   D. Levofloxacin 500 mg once daily plus metronidazole 500 mg twice daily plus omeprazole 20 mg twice daily for 21 days.

III. UPPER GI BLEEDING

A. Causes of upper GI bleeding
   1. Peptic ulcer disease (40%–70%) due to NSAIDs and low-dose aspirin use or *H. pylori*
   2. Esophagitis
   3. Erosive disease
   4. Esophageal varices
   5. Mallory-Weiss tear (longitudinal mucosal lacerations in the lower esophagus or upper stomach)
   6. Neoplasm
   7. Stress ulcers (critically ill patients)

B. Clinical Symptoms and Presentation
   1. Hematemesis or "coffee-ground" emesis
   2. Hematochezia
   3. Nausea, vomiting
   4. Melena
   5. Shock (tachycardia, clammy skin)
   6. Hypotension
   7. Associated organ dysfunction (renal, hepatic, cardiac, cerebral hypoperfusion)

Box 2. Clinical Predictors of Death Associated with Nonvariceal Upper GI Bleeding

Advanced age (> 75 yr at highest risk)	Elevated serum urea
Blood in gastric aspirate	Red blood on rectal examination
Continued bleeding or rebleeding	SCr > 150 µmol/L (1.7 mg/dL)
> 1 comorbid condition	Sepsis
Elevated aminotransferases	Shock or hypotension

Box 3. Predictors of Persistent or Recurrent Upper GI Bleeding

Age > 65 yr	Gastric or duodenal ulcer
Blood in gastric aspirate	Hematemesis
Coagulopathy	Initial hemoglobin < 10 g/dL or hematocrit < 30%
Comorbid illness	Location of ulcer on superior or posterior wall
Endoscopic findings:	Melena
Active bleeding on endoscopy	Ongoing bleeding
Presence of high-risk stigmata	Red blood on rectal examination
Adherent clot	Shock (systolic blood pressure < 100 mm Hg)
Erratic mental status	Ulcer size ≥ 2 cm

C. Management of ulcer-related GI bleeding
   1. Volume resuscitation and hemodynamic stabilization
      a. Placement of one or two large-bore intravenous catheters
      b. Replacement with crystalloid such as 0.9% normal saline is preferred; colloids such as blood can be given after initial resuscitation in patients with hemoglobin of less than 7 g/dL to maintain a hemoglobin concentration of 8–10 g/dL.
   2. Risk stratification
      a. Clinical signs and symptoms
      b. Use of clinical scoring scales such as Glasgow-Blatchford scores to determine the risk of early rebleeding and the need for urgent versus nonemergency intervention. Patients with low risk of rebleeding can be discharged after endoscopy.
      c. Placing an NG tube for aspiration can be considered but is not required.
      d. Endoscopy (within 24 hours if possible, 12 hours with high-risk clinical features)
      e. Assessment of comorbid illnesses (liver disease, coagulopathies, cardiac status)
      f. Predictive factors of death with upper GI bleed are listed in Box 2. Predictors of persistent or recurrent GI bleeding are listed in Box 3.

3. Endoscopic therapy
    a. Endoscopic therapy is associated with reductions in rebleeding, need for surgery, and mortality. Perform within 12–24 hours of presentation.
    b. Observation of low-risk stigmata (a clean-based ulcer or a nonprotuberant pigmented dot in an ulcer bed) is not an indication for hemostatic therapy.
    c. Clots visible in an ulcer bed should be irrigated, with treatment of underlying lesions
    d. The presence of high-risk stigmata warrants immediate hemostatic therapy.
4. Endoscopic strategies
    a. The combination of injection and coaptive therapy is the most efficacious; the use of either technique plus pharmacotherapy is superior to monotherapy.
    b. Sclerotherapy: No single solution for injection is superior to another.
        i. Epinephrine with or without ethanolamine is inferior by itself. Combine with another endoscopic therapy.
        ii. Cyanoacrylate
        iii. Thrombin
        iv. Sodium tetradecyl sulfate
        v. Polidocanol
    c. Thermal coaptive therapy: No single method is superior to another.
        i. Heater probe thermocoagulation
        ii. Multipolar electrocoagulation
        iii. Laser coagulation (not often used because of cost)
        iv. Argon plasma coagulation
    d. Placement of hemostatic clips
5. Pharmacotherapeutic management of nonvariceal upper GI bleeding
    a. Remove medications that are contributing to bleeding (e.g., NSAIDs).
    b. PPI therapy
        i. Use of a pre-endoscopic dose (80-mg intravenous bolus, followed by an 8-mg/hour intravenous infusion) of PPI may be considered. This does not result in reduced mortality, surgery, or rate of rebleeding, but it can reduce the lesion size, the possibility of finding a high-risk lesion, and the need for endoscopic therapy. PPIs may be given if endoscopy will be delayed or cannot be performed.
        ii. Bolus 80 mg plus a continuous infusion of 8 mg/hour for 72 hours after endoscopic therapy for patients with active bleeding or nonbleeding visible vessel or with adherent clot. Intravenous pantoprazole or esomeprazole can be used; most data are with intravenous omeprazole (used in Europe).
        iii. Intermittent PPI therapy (80-mg intravenous bolus followed by 40 mg intravenously twice daily) is safe and effective and may reduce costs associated with continuous intravenous infusions (Am J Health Syst Pharm 2017;74:109-16).
        iv. Associated with decreases in rebleeding, mortality, and need for surgery in patients with active bleeding who have undergone successful endoscopic intervention.
        v. Oral once-daily PPI therapy can be used for patients with a flat spot or clean-based ulcer.
    c. The use of H_2RAs or somatostatin-octreotide is not recommended.
    d. Test for *H. pylori* and treat if results are positive. If result are negative, then retest. There is no need for a PPI after eradication.
    e. Assess the need for continued secondary prevention with PPI therapy. If needed, a single daily oral dose of a PPI is recommended.
    f. Assess the need for NSAID or aspirin use. If NSAID therapy is needed, then use of a COX-2 inhibitor plus a PPI is recommended, barring any significant CV risk. Otherwise, a PPI should be used.

g. If the use of low-dose aspirin is required, reinitiate when CV risk is thought to outweigh GI risk. Use a PPI and reinitiate aspirin within 1–3 days, if not within 1 week. Clopidogrel has a higher rate of rebleeding than aspirin.
h. Long-term PPI therapy is recommended for ulcers not associated with NSAIDs or *H. pylori*.

D. Prophylaxis of SRMD in critically ill patients
1. Stress-related injury: Superficial diffuse upper GI ulceration
2. Stress ulcer: Deeper mucosal ulceration; may lead to bleeding and hemodynamic compromise
3. Contributing factors to SRMD development
a. Hypoperfusion of the GI tract
b. Altered susceptibility to gastric acid
c. Loss of defense mechanisms: mucous/bicarbonate layer, prostaglandins, cellular renewal
d. Alterations in gastric motility; may affect absorption of drugs
4. Pharmacologic prevention
a. Not routinely recommended in non–intensive care unit settings
b. Recommended in patients in an intensive care unit with the risk factors in Box 4.

Box 4. Risk Factors for Initiation of Prophylaxis for SRMD in Intensive Care Units

Mechanical ventilation > 48 hr[a]	Two or more of the following:
Coagulopathy (platelet count < 50,000/mm^3, INR > 1.5)[a]	Sepsis syndrome
Thermal injury (> 35% BSA)	ICU stay > 1 wk
Severe head or spinal cord injury	Occult bleeding
GI bleeding or ulceration within past year Multiple trauma (injury severity score > 16) Perioperative transplant period	High-dose corticosteroids (250 mg of hydrocortisone equivalent)
Low intragastric pH	Hepatic failure
Major surgery (lasting > 4 hr)	Acute renal insufficiency
Acute lung injury	Hypotension
	Anticoagulation

[a]Independent risk factors for SRMD.

BSA = body surface area; ICU = intensive care unit; INR = international normalized ratio; SRMD = stress-related mucosal disease.

5. Preventive treatment options
a. Antacids require several oral doses per day or administration by enteral tube. Diarrhea, constipation, and electrolyte abnormalities are possible.
b. Sucralfate
i. Provides a direct mucosal barrier; modulates pepsin, mucus activity, bicarbonate secretion, and tissue growth repair
ii. Requires many oral doses or administration by enteral tube. May lead to aluminum accumulation and constipation. Possibility of binding to other drugs in GI tract. No effect on platelet count and associated with lower rates of pneumonia development.
iii. General efficacy regarding bleeding considered similar to that of H_2RAs
c. H_2RAs
i. Reduce gastric acid secretion by inhibition of histamine stimulation of the parietal cell; development of tolerance or tachyphylaxis with continued use.
ii. Considered efficacious in the prevention of clinically significant bleeding; oral, intravenous intermittent dosing, and continuous infusion are all possible options. High-dose intravenous (ranitidine, cimetidine, or famotidine) use can be considered first-line therapy. Cimetidine is the only H_2RA that is FDA approved for SRMD prevention.

iii. Associated with CNS adverse effects and the rare development of thrombocytopenia; require adjustment for renal dysfunction

d. Proton pump inhibitors
   i. The American Society of Health-System Pharmacists guidelines include minimal recommendations for PPI use because of the lack of data at that time; however, PPIs are commonly used for SRMD prevention.
   ii. PPIs are similar to H_2RAs in safety and efficacy.
   iii. Oral or intravenous routes may be used. Alternative formulations exist for patients with difficulty swallowing or with feeding tubes (see section on GERD).
   iv. Oral PPIs are as efficacious as intravenous PPIs for maintaining equivalent pH
   v. Intravenous PPI therapy is generally considered equivalent to high-dose intravenous H_2RA therapy.
   vi. In a recent trial, 3298 patients with unplanned intensive care unit admission were randomized to receive either pantoprazole 40 mg intravenously daily or placebo. Mortality at 90 days (primary end point; RR 1.02; 95% CI, 0.91–1.13) and composite event rate, including clinically important GI bleeding, pneumonia, Clostridioides difficile infection, or myocardial infarction (RR 0.96; 95% CI, 0.83–1.11), were similar between groups. Clinically important GI bleeding occurred in 2.5% of patients receiving pantoprazole compared with 4.2% of patients receiving placebo (RR 0.58; 95% CI, 0.4–0.86) (N Engl J Med 2018;379:2199-208).

IV. INFLAMMATORY BOWEL DISEASE

A. Background
   1. Inflammatory bowel disease (IBD) includes both UC and CD. In some instances, UC may be indistinguishable from CD, called *indeterminate* or *intermediate colitis*.
   2. Pathophysiology: The exact cause of continuing inflammation of the GI mucosa is unknown, but it is thought that the inflammation is secondary to an antigen-driven response.
   3. Contributing factors
      a. Defects in the intestinal epithelial barrier and immune system
      b. There is a definite genetic association; first-degree relatives of affected patients have a 4–20-fold greater risk of developing IBD.
      c. Environmental
         i. NSAIDs: Worsen IBD, probably secondary to alteration of epithelial barrier
         ii. Smoking: Worsens CD; associated with improvement in UC symptoms
         iii. Luminal bacteria: Endogenous intestinal bacteria thought to be highly involved in stimulating the intestinal inflammatory response observed in IBD
         iv. Dietary antigens may also contribute to ongoing inflammation.
      d. Various proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor (TNF), contribute to the ongoing inflammatory process.

B. Clinical features
   1. Presenting symptoms common to UC and CD include fever, abdominal pain, diarrhea (may be bloody, watery, or mucopurulent), rectal bleeding, and weight loss. Symptoms can vary depending on disease location. See Table 8 for the clinical features of IBD.

Table 8. Clinical Features of Inflammatory Bowel Disease

Clinical Findings	Ulcerative Colitis	Crohn Disease
Bowel involvement	Confined to rectum and colon Terminal ileal involvement (backwash ileitis) in a minority of patients	May be anywhere from mouth to anus (66% of cases located in ileum)
Perianal involvement	Unlikely	Yes
Depth of ulceration	Superficial	May extend to submucosa or deeper
Continuous inflammation	Very common	Rarely, a patchy, "cobblestone" appearance
Histology	Nontransmural, crypt abscesses	Transmural lesions, granulomas
Fistula, perforation, or strictures	Very uncommon	Yes
Development of toxic megacolon	Yes	No
Malabsorption or malnutrition	Rare	Yes, often vitamin deficiencies; possible growth retardation in children
Risk factor for colorectal cancer	Yes	Uncommon unless disease affects colon
Pseudopolyps	Common	Fairly uncommon

2. Systemic manifestations
    a. Both UC and CD can present with concurrent systemic manifestations.
    b. Hepatobiliary: primary sclerosing cholangitis, cholangiocarcinoma, hepatitis, cirrhosis, cholelithiasis, steatosis
    c. Rheumatologic arthritis, sacroiliitis, ankylosing spondylitis
    d. Dermatologic: erythema nodosum, aphthous ulcers, pyoderma gangrenosum
    e. Ocular: iritis or uveitis, episcleritis
3. Gauging clinical severity
    a. Ulcerative colitis severity can be determined using Table 9 (based on Truelove and Witt criteria)

Table 9. Clinical Severity of Ulcerative Colitis

Mild	Moderate	Severe	Fulminant
≤4 stools/day (±blood) No fever, anemia, or tachycardia Normal ESR	> 4 stools/day (±blood) Minimal signs of systemic toxicity	> 6 stools/day with blood Body temperature > 99.5°F HR > 90 beats/min ESR > 30 mm/hr Hgb < 75% of normal Abdominal tenderness Bowel wall edema	> 10 stools/day with continuous blood Body temperature > 99.5°F HR > 90 beats/min ESR > 30 mm/hr Transfusions required Abdominal pain Dilated colon

ESR = erythrocyte sedimentation rate; Hgb = hemoglobin; HR = heart rate.

b. Crohn disease
    i. Mild-moderate: tolerates oral administration; absence of fever, dehydration, and abdominal tenderness; less than 10% weight loss
    ii. Moderate-severe: failed treatment of mild-moderate; anemia, nausea and vomiting, or considerable weight loss usually present
    iii. Severe: no response to outpatient steroids; high temperature, abdominal pain, persistent vomiting; possible obstruction, abscess, cachexia, rebound tenderness

4. General management considerations
    a. Rule out possible infectious causes of bloody diarrhea, especially *C. difficile*, in patients with acute symptoms.
    b. Elevated concentrations of fecal lactoferrin and fecal calprotectin indicate inflammation and help differentiate patients with IBD from those with IBS. These concentrations may also be used to monitor disease activity and therapy response.
    c. Most patients will undergo colonoscopy to confirm the diagnosis and extent of disease. Computed tomography enterography or magnetic resonance enterography can be considered to evaluate inflammation within the ileum in CD.
    d. Surgery is a viable option when complications (abscess, fistula, perforation) occur or when fulminant disease is unresponsive to medical treatment.
    e. Distribution and severity of disease will dictate the initial treatment choice.
    f. Treatment is generally initiated with induction therapy. These treatments are used to acutely control symptoms and inflammation. Once symptoms are controlled, longer-term maintenance therapy is used to control symptoms and inflammation, together with systemic complications. Most patients will require maintenance therapy because of the high incidence of relapse after induction therapy; the relapse rate is 35%–80% at 2 years for CD and 50%–70% at 1 year for UC.

C. Medical management of IBD: adjunctive therapies
1. Caution in active disease; reduction in motility may precipitate toxic megacolon
2. Loperamide (Imodium) can be useful for proctitis or diarrhea; 2 mg after each loose stool (16 mg/day maximum)
3. Antispasmodics
    a. Dicyclomine (Bentyl), 10–40 mg orally four times daily
    b. Propantheline (Pro-Banthine), 7.5–15 mg orally three times daily
    c. Hyoscyamine (Levsin), 0.125–0.25 mg orally/slow release every 4 hours as needed
4. Cholestyramine (Questran): for bile salt–induced diarrhea after ileal resection

D. Medications used to treat IBD
1. Selection of treatment is based on disease location and severity.
2. Aminosalicylates
    a. Used for both induction and maintenance of remission
    b. Sulfasalazine: prototype agent (Azulfidine, Azulfidine-EN)
        i. Sulfasalazine is cleaved by colonic bacteria to the active portion (5-aminosalicylate) and the inactive carrier molecule sulfapyridine.
        ii. Efficacy is best in colonic disease because of colonic activation of the drug.
        iii. Dose-related adverse effects (due to the sulfapyridine portion): GI disturbance, headache, arthralgia, folate malabsorption
        iv. Idiosyncratic adverse effects: rash, fever, pneumonitis, hepatotoxicity, bone marrow suppression, hemolytic anemia, pancreatitis, decreased sperm production in men
        v. Avoid in patients with a sulfa allergy.

vi. Dosed 4–6 g/day for induction and 2–4 g/day for maintenance; available as immediate-release and enteric-coated products. Doses should be titrated beginning at 500–1000 mg once or twice daily to avoid adverse effects.

c. 5-Aminosalicylates (non–sulfa containing)
   i. Generally better tolerated than sulfasalazine; first line in mild-moderate UC and CD
   ii. Product selection depends on location of disease. Available formulations are listed in Table 10
   iii. Olsalazine is associated with secretory diarrhea in up to 25% of patients.
   iv. Rare instances of nephrotoxicity with use of 5-aminosalicylates

Table 10. Aminosalicylate Formulations

Drug	Trade Names	Formulation	Strength	Daily Dose Range (g)	Site of Action
Mesalamine	Rowasa[a]	Enema	4 g/60 mL	4	Rectum, terminal colon
	Delzicol Asacol HD, Zaldyon	Delayed-release capsule Delayed-release tablet	400 mg 800 mg	1.6–4.8	Distal ileum, colon
	Canasa	Suppository	1000 mg	1	Rectum
	Pentasa	Controlled-release capsule	250 mg 500 mg	2–4	Small bowel, colon
	Lialda	Multimatrix (MMX) delayed-release tablet	1.2 g	2.4–4.8 (once daily)	Colon
	Apriso	Intellicor delayed- and extended-release capsule	0.375 g	0.375–1.5 (once daily)	Colon
Olsalazine	Dipentum	Dimer of mesalamine (capsule)	250 mg	1–3	Colon
Balsalazide	Colazal Giazo	Capsule Tablet	750 mg 1100 mg	2–6.75	Colon

[a]Generic mesalamine enema available.

3. Corticosteroids
   a. Work quickly to suppress inflammation during acute flares
   b. They have no role in maintenance therapy; however, more than 50% of patients with severe disease may become steroid-dependent.
   c. Budesonide is about 15-fold more potent than prednisone; because of its high first-pass metabolism and limited systemic exposure, allow a 2-week overlap when changing from prednisone to budesonide to prevent adrenal insufficiency. It is formulated to release in the terminal ileum and treats only terminal ileal and ascending colonic disease.
   d. Adverse effects (systemic therapy): adrenal suppression, glucose intolerance, hypertension, sodium/water retention, osteoporosis, cataracts, and impaired wound healing. Systemic adverse effects are minimal with budesonide use.
   e. Available corticosteroid formulation are listed in Table 11

Table 11. Corticosteroid Preparations

Route	Agents	Dose	Comments
Oral	Prednisone Prednisolone	20–60 mg/day	Taper as soon as possible
	Budesonide capsule (Entocort EC 3 mg) Budesonide tablet (Uceris 9 mg)	9 mg/day PO; then 6 mg/day Can be continued for up to 3 mo 9 mg/day in the morning for 8 wk	Minimal absorption, minimal systemic adverse effects; indicated for treatment and maintenance of mild-moderate active CD involving terminal ileum or ascending colon
Intravenous	Hydrocortisone Methylprednisolone	100 mg every 8 hr 15–48 mg/day	7- to 10-day course; change to PO when gut is functional
Topical (rectal)	Cortenema (100 mg/60 mL) Cortifoam (90 mg/applicator) Anucort-HC 25 mg Proctocort 30 mg	100 mg HS 90 mg/day BID 25–50 mg PR BID	Hydrocortisone-based products Used for patients with distal disease Suppositories; use for proctitis
	Uceris rectal foam	2 mg BID x 2 wk; then daily x 4 wk	For induction of remission of mild to moderate distal UC

BID = twice daily; CD = Crohn disease; HS = at bedtime; PO = by mouth; PR = rectally; UC = ulcerative colitis.

4. Immunomodulators
    a. Mercaptopurine (Purinethol), azathioprine (Imuran, Azasan; prodrug of mercaptopurine), methotrexate, or tofacitinib (Xeljanz)
    b. Doses: Azathioprine 2–2.5 mg/kg/day orally, mercaptopurine 1–1.5 mg/kg/day orally, methotrexate 15–25 mg/week intramuscularly (CD only)
    c. Indicated only for maintenance because of long onset of action (3–15 months)
    d. Use can result in a steroid-sparing effect.
    e. Azathioprine and mercaptopurine are metabolized by the enzyme thiopurine methyltransferase (TPMT); reduced expression of TPMT can result in slower metabolism and increased toxicity. TPMT activity or TPMT genotype or phenotype should be determined before initiating therapy.
    f. Adverse reactions
        i. Azathioprine and mercaptopurine: pancreatitis (3%–15%), bone marrow suppression, nausea, diarrhea, rash, possible hepatotoxicity. Risk of hepatosplenic T-cell lymphoma, especially in younger male patients or if combined with a TNFα antagonist.
        ii. Methotrexate: bone marrow suppression, nausea, diarrhea, rash, pulmonary toxicity, hepatotoxicity
    g. Tofacitinib (Xeljanz)
        i. Oral Janus kinase (JAK) inhibitor indicated for moderate to severe UC
        ii. Induction dosing: 10 mg orally twice daily for at least 8 weeks
        iii. Maintenance dosing: 5–10 mg orally twice daily depending on response
        iv. Discontinue if response is inadequate after 16 weeks of treatment with 10 mg twice daily.

v. Dose adjustments: If receiving a strong CYP3A4 inhibitor or moderate CYP3A4 inhibitor and a strong CYP2C19 inhibitor, or if moderate to severe renal impairment or moderate hepatic impairment: Reduce 10-mg twice-daily dose to 5 mg twice daily; reduce 5-mg twice-daily dose to 5 mg once daily. If lymphocyte count or absolute neutrophil count is less than 500 cells/mm3, discontinue tofacitinib. If absolute neutrophil count is 500–1000 cells/mm3, reduce dose as earlier and resume previous dose when absolute neutrophil count is greater than 1000 cells/mm3. Interrupt dosing for hemoglobin less than 8 g/dL or a reduction of more than 2 g/dL, and restart dosing when hemoglobin normalizes. Interrupt therapy if patient experiences a serious infection.

vi. In the OCTAVE Induction 1 and 2 trials, patients with moderate to severe active UC despite prior conventional therapy or TNF inhibitor therapy received tofacitinib 10 mg or placebo twice daily for 8 weeks. In OCTAVE 1, 18.5% and 8.2% of patients achieved remission with tofacitinib and placebo, respectively ($p=0.007$). In OCTAVE 2, 16.6% and 3.6% achieved remission, respectively ($p<0.001$). OCTAVE Sustain reported remission at 52 weeks in 34.3% of patients receiving 5 mg of tofacitinib twice daily, 40.6% receiving 10 mg twice daily, and 11.1% receiving placebo ($p<0.001$ both comparisons with placebo).

vii. Tofacitinib has been associated with nasopharyngitis, upper respiratory tract infection, increased blood creatine phosphokinase, and cholesterol concentrations; rash; headache; diarrhea; and herpes zoster. Tofacitinib is also associated with serious infections such as tuberculosis, and patients should be screened before starting therapy. Lymphocytopenia, neutropenia, and low hemoglobin can occur. Check lymphocytes at baseline and every 3 months, and check neutrophil and hemoglobin concentrations at baseline, after 4–8 weeks of therapy, and then every 3 months. Tofacitinib has also been associated with malignancies and GI perforation.

vii. Tofacitinib carries a warning for the development of deep venous thrombosis, pulmonary embolism, and arterial thrombosis in patients with rheumatoid arthritis who are 50 and older with one or more cardiovascular risk factors and who are taking higher-than-recommended doses of tofacitinib.

ix. Tofacitinib is associated with serious infections that may result in hospitalization or death, especially in patients receiving concomitant methotrexate or corticosteroids.

5. Biologic agent (infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab, ustekinumab) baseline evaluation
   a. Comprehensive metabolic panel, liver function tests, complete blood cell count
   b. Viral hepatitis screening
   c. Tuberculosis screening
6. Infliximab (Remicade)
   a. Chimeric monoclonal antibody against TNFα
   b. Indicated for both CD and UC
      i. Moderate-severe active disease
      ii. Fistulizing CD
      iii. Maintenance of moderate-severe disease
   c. Available as intravenous infusion only; expensive
   d. Studies of patients whose conventional therapy failed show that clinical response is about 40%–80% according to disease activity scores.
   e. Dosing: Moderate-severe active disease or fistulizing disease: 5 mg/kg as single dose, followed by 5 mg/kg at 2 and 6 weeks, then every 8 weeks as maintenance. Patients losing response with time can be treated with a 10 mg/kg dose.
   f. Therapeutic drug monitoring: Minimal "therapeutic" target trough concentrations: infliximab 7.5 mcg/mL or greater according to the guidelines

g. Adverse reactions
    i. Infusion related: hypotension, fever, chills, urticaria, pruritus; infuse over at least 2 hours (may pretreat with acetaminophen and/or antihistamine)
    ii. Delayed hypersensitivity: fever, rash, myalgia, headache, or sore throat 3–10 days after administration
    iii. Infection: reactivation of latent infections (bacterial, including disseminated tuberculosis, fungal, and sepsis); do not give to patients with active infections. Tuberculosis should be ruled out before any biologic agents are initiated.
    iv. Heart failure exacerbations: contraindicated in New York Heart Association class III/IV heart failure; do not exceed 5-mg/kg dose in other patients with chronic heart failure.
    v. Antibody induction: Up to 50% of patients may develop antinuclear antibodies; 19% may develop anti-double-stranded DNA antibodies.
    vi. Bone marrow suppression (pancytopenia)
    vii. Black box warning applies to all TNFα antagonists. Unusual cancers have been reported in children and teenage patients taking TNF blockers. Hepatosplenic T-cell lymphoma has occurred mostly in teenaged or young adult males with CD or UC who were taking infliximab and azathioprine or mercaptopurine.
    viii. Hepatitis (reactivation of hepatitis B virus [HBV], autoimmune hepatitis): Discontinue use if liver function tests rise to more than 5 times the upper limit of normal (ULN).
    ix. Vasculitis with CNS involvement

7. Adalimumab (Humira)
    a. Fully humanized antibody to TNFα; therefore, theoretically, there is a reduced risk of development of antibodies
    b. Indicated for both induction and maintenance therapy for moderate-severe active CD and UC in patients unresponsive to conventional therapy; also indicated for patients who no longer respond to infliximab
    c. Dosing: induction, 160 mg subcutaneously on day 1 (given as four separate 40-mg injections) or two 40-mg/day injections for 2 consecutive days, followed by 80 mg subcutaneously 2 weeks later (day 15). Next, can decrease dose to 40 mg subcutaneously every other week starting on day 29 of therapy
    d. Therapeutic drug monitoring: Minimal "therapeutic" trough concentration of adalimumab of 5 mcg/mL or greater
    e. Efficacy
        i. Complete remission rates at week 4 range from 21% to 54%.
        ii. Efficacy rates for maintenance therapy are 56%–79% at week 4 and 36%–46% at week 56.
        iii. The adverse effect profile of adalimumab is similar to that of infliximab.
8. Certolizumab (Cimzia)
    a. Humanized monoclonal antibody fragment to TNFα linked to polyethylene glycol, with murine-complimentary determining regions
    b. Indicated for maintenance therapy for moderate-severe active CD in patients unresponsive to conventional therapy
    c. Dosing: induction, 400 mg subcutaneously, then 400 mg subcutaneously at weeks 2 and 4; maintenance dose of 400 mg subcutaneously every 4 weeks
    d. Therapeutic drug monitoring: Evidence is sparse; however, a certolizumab pegol trough concentration of 20 mcg/mL or greater has been suggested as a minimal "therapeutic" target.

e. Efficacy
    i. Patients with a C-reactive protein concentration greater than 10 mg/L have the best response. Up to 37% response at 6 weeks versus 26% for placebo.
    ii. Up to 62% of patients with an initial response and a C-reactive protein concentration greater than 10 mg/L may be maintained in remission at 26 weeks.
    iii. The certolizumab adverse effect profile is similar to that of other TNFα antagonists.

9. Golimumab (Simponi)
    a. Human IgG1κ monoclonal antibody
    b. Indicated for moderate to severe UC in patients intolerant of previous therapies or requiring continuous steroid therapy
    c. Dosing: 200 mg subcutaneously at week 0, 100 mg at week 2, and 100 mg every 4 weeks thereafter
    d. Efficacy
        i. In moderate to severe UC, clinical response at 6 weeks was 51% with golimumab versus 30% with placebo. Clinical remission at 6 weeks was 18% and 6% with golimumab and placebo, respectively.
        ii. Continued clinical response for 54 weeks was 50% with golimumab and 31% with placebo.
    e. Adverse effects: toxicity profile similar to that of other TNFα antagonists
10. Natalizumab (Tysabri)
    a. Humanized monoclonal antibody that antagonizes integrin heterodimers and inhibits α4 integrin-mediated leukocyte adhesion
    b. Indicated for inducing and maintaining clinical response and remission in adult patients with moderate-severe active CD who have had an inadequate response to, or are unable to tolerate, conventional therapies and inhibitors of TNFα. John Cunningham (JC) virus serum antibody test should be completed before and every 6 months during natalizumab therapy. Treatment should be discontinued if the result is positive.
    c. Dosing
        i. Must enroll in the TOUCH program before the drug is dispensed because of its association with progressive multifocal leukoencephalopathy
        ii. Induction and maintenance doses are both 300 mg intravenously every 4 weeks. If there is no effect after 12 weeks or inability to discontinue steroids within 6 months of beginning therapy, treatment should be discontinued.
    d. Efficacy
        i. The ENACT 1 and 2 trials showed similar results for natalizumab and placebo at 10 weeks (56% vs. 49%; p=0.05); however, those who initially responded had rates of sustained response (61% vs. 28%; p=0.001) at week 36.
        ii. Can also improve quality of life in patients who initially respond after 48 weeks of treatment
    e. Adverse effects
        i. Natalizumab is associated with the development of progressive multifocal leukoencephalopathy. Monitor for mental status changes during treatment. Consider magnetic resonance imaging and lumbar puncture if mental status changes or weakness is observed.
        ii. Because of a potential for hepatotoxicity, monitor for jaundice or other signs of liver disease.
        iii. Increased risk of infection
        iv. Infusion-related reactions: Observe patient for 1 hour after infusion.
        v. The drug should not be used in combination with TNFα inhibitors or immunosuppressants.
11. Vedolizumab (Entyvio)
    a. Humanized monoclonal antibody that targets α4β7-integrin–mediated leukocyte adhesion
    b. Indicated use as induction and maintenance therapy for patients with UC and CD for whom other therapies, including TNFα antagonists, have failed

c. Induction and maintenance doses are both 300 mg intravenously given at 0, 2, and 6 weeks and then every 8 weeks. Discontinue if there is no evidence of improvement at 14 weeks.
d. The GEMINI I study showed efficacy in induction and maintenance for moderate-severe UC with a clinical response rate of 47% versus 25% versus placebo at 6 weeks ($p<0.001$). The GEMINI II study of induction and maintenance of moderate to severe CD showed remission rates of 14.5% vs. 6.8% for placebo at 6 weeks ($p=0.02$).
e. Safety profile is similar to that of natalizumab, with the exception of a lower risk of progressive multifocal leukoencephalopathy, because vedolizumab's mechanism is more specific for gut-based integrin. There is no required prescribing program.

12. Ustekinumab (Stelara)
    a. Monoclonal antibody to the p40 subunit of interleukin 12 and interleukin 23 (anti-IL-12/23)
    b. Indicated for moderate to severely active CD and UC after the failure of corticosteroids, thiopurines, methotrexate, or TNF inhibitors
    c. Induction dosing: 260 mg for patients weighing less than 55 kg, 390 mg for those weighing more than 55-85 kg, and 520 mg for those weighing more than 85 kg intravenously at week 0
    d. Maintenance dosing: 90 mg subcutaneously every 8 weeks
    e. The UNITI-1 study of patients with CD who had received a TNF inhibitor with inadequate response or intolerable adverse effects. The UNITI-2 study included patients with active CD and treatment failure or intolerable adverse effects to immunosuppressant or glucocorticoid therapy. Ustekinumab 130-mg dose and a weight-based 6-mg/kg dose resulted in response at week 6 more often than placebo (UNITI-1 34.3%, 33.7%, and 21.5%, respectively; UNITI-2 51.7%, 55.5%, and 28.7%, respectively; $p<0.05$ for all comparisons with placebo). Maintenance doses every 8 or 12 weeks resulted in remission at week 44 in 53.1% and 48.8% of patients compared with 35.9% receiving placebo ($p<0.05$ vs. placebo).
    f. The UNIFI study evaluated ustekinumab 130 mg, ustekinumab weight-based dosing (6 mg/kg), or placebo in 961 patients with moderate to severe UC whose conventional or biologic therapy had failed. The ustekinumab 130-mg and weight-based doses resulted in remission at week 8 in more patients than placebo (15.6%, 15.5%, and 5.3%, respectively; $p<0.001$ for both comparisons). The 523 patients who achieved remission were randomized to maintenance therapy with ustekinumab 90 mg every 8 or 12 weeks, or placebo. At 44 weeks, ustekinumab resulted in remission in 43.8% (90 mg every 8 weeks), 38.4% (90 mg every 12 weeks), and 24% (placebo) ($p<0.05$ vs. placebo). Adverse effects were similar between ustekinumab and placebo.
    g. Common adverse effects were vomiting with induction therapy and nasopharyngitis, injection-site erythema, vulvovaginal candidiasis, bronchitis, pruritus, urinary tract infection, and sinusitis with maintenance treatment. As with other biologic therapies, serious infections include tuberculosis; therefore, screening for tuberculosis is recommended before starting therapy.

E. Medical management of UC: Treatment is selected according to disease location and severity.
    1. Guideline definitions of UC distribution
        a. Distal disease: Distal to splenic flexure (may use oral/systemic or topical [rectal] therapy)
        b. Extensive disease: Proximal to splenic flexure (requires systemic/oral therapy)
    2. Mildly active UC
        a. Topical aminosalicylates are recommended for induction of remission for ulcerative proctitis (strong recommendation, high-quality evidence) and left-sided colitis (strong recommendation, moderate-quality evidence). An oral aminosalicylate in combination with a topical aminosalicylate is more effective than oral therapy alone (conditional recommendation, low-quality evidence). Oral aminosalicylate therapy should be used for mildly active extensive colitis (strong recommendation, moderate-quality evidence).

b. Patients with mildly active UC who are intolerant of or who have responded to aminosalicylate therapy should receive oral budesonide (Uceris) for left-sided disease (strong recommendation, moderate-quality evidence) or systemic corticosteroids for any extent of UC (strong recommendation, low-quality evidence) to induce remission.
c. Continued topical and/or oral aminosalicylate therapy, but not corticosteroids, should be used to maintain remission (strong recommendation, moderate-quality evidence).

3. Moderately to severely active UC
   a. In moderately active UC, oral budesonide is recommended to induce remission (strong recommendation, moderate-quality evidence).
   b. In moderately to severely active UC, systemic steroids, anti-TNF therapy (adalimumab, golimumab, or infliximab), vedolizumab, tofacitinib, or ustekinumab may be used to induce remission. (strong recommendations, moderate to high quality of evidence).
   c. Infliximab for induction of remission should be combined with thiopurine therapy (strong recommendation, moderate-quality evidence for azathioprine).
   d. Patients whose induction with anti-TNF therapy has failed should receive vedolizumab, tofacitinib, or ustekinumab to induce remission (strong recommendation, moderate-quality evidence).
   e. A patient who achieves remission with a biologic agent should be continued on that agent to maintain remission (strong recommendation, moderate-quality evidence). Patients whose remission is achieved using corticosteroids may receive thiopurine therapy to maintain remission (conditional recommendation, low-quality evidence).
4. Hospitalized patients with acute severe UC
   a. Methylprednisolone 40–60 mg/day or the equivalent intravenously is recommended to induce remission (strong recommendation, low-quality evidence).
   b. If a patient's UC does not respond after 3–5 days of intravenous corticosteroid therapy, rescue therapy with infliximab or cyclosporine is recommended (strong recommendation, moderate-quality evidence).
   c. If remission is achieved with infliximab, continue therapy for maintenance. If remission is achieved with cyclosporine, maintain remission with a thiopurine or vedolizumab.

F. Medical management of CD
1. Treatment is selected according to disease location and severity.
2. Mild-moderate active disease: First line for ileal, ileocolonic, or colonic disease
   a. Oral aminosalicylate (mesalamine 3.2–4 g/day or sulfasalazine 6 g/day) is commonly used but considered minimally effective.
   b. Budesonide 9 mg/day is preferred for terminal ileal or ascending colonic disease.
   c. Metronidazole 10–20 mg/kg/day may be used in patients not responding to oral aminosalicylates, but it is generally more effective in patients with perianal or colonic disease.
   d. Ciprofloxacin 1 g/day is considered as effective as mesalamine (generally, second line), but is usually more effective in perianal or colonic disease and is typically used in combination with metronidazole.
3. Moderate-severe disease
   a. Corticosteroids (prednisone 40–60 mg/day or budesonide 9 mg/day if terminal ileal involvement) until resolution of symptoms and resumption of weight gain
   b. Anti-TNFα agents in combination with thiopurines are the preferred therapies for induction of remission for moderate to severe CD. Thiopurine monotherapy or methotrexate is not recommended to induce remission in moderate to severe active CD.
      i. Infliximab 5 mg/kg is an alternative first-line treatment (improvement in up to 80% of patients). Infliximab can be combined with azathioprine in patients whose therapy with aminosalicylates and corticosteroids has failed and who are naive to biologic agents. This combination is superior to each drug given alone; however, there is a risk of hepatosplenic T cell lymphoma.

ii. Certolizumab 400 mg subcutaneously and then 400 mg subcutaneously at weeks 2 and 4, or adalimumab 160 mg subcutaneously initially followed by 80 mg subcutaneously 2 weeks later, can also be considered, particularly in patients with C-reactive protein values greater than 10 mg/L.
iii. Adalimumab can be used as initial therapy or for patients who no longer respond to infliximab therapy because they developed antibodies to infliximab.

c. Vedolizumab 300 mg (or natalizumab) intravenously every 4 weeks can be considered for patients who did not respond to any other conventional medical therapy.
d. Ustekinumab 260-520 mg intravenously on the basis of patient weight, followed by 90 mg subcutaneously every 8 weeks can be used for patients whose conventional or inhibitor therapy has failed.
e. Methotrexate maintenance therapy (15–25 mg/week intramuscularly or subcutaneously) is effective in patients whose active disease has responded to intramuscular methotrexate and who have steroid-dependent or steroid-refractory disease.

4. Severe disease
   a. Severe symptoms despite oral corticosteroids or infliximab therapy
   b. Assess need for surgical intervention (mass, obstruction, and abscess).
   c. Administer intravenous corticosteroids (40–60 mg of prednisone equivalent).
   d. Parenteral nutrition may be needed after 5–7 days.
   e. Possibly use intravenous cyclosporine if steroids fail.
5. Maintenance therapy
   a. There is no role for long-term corticosteroid use, but budesonide can be used for up to 3 months in patients with mild-moderate disease with ileal involvement.
   b. Azathioprine/mercaptopurine or infliximab, or the combination, can be used after induction with corticosteroids.
   c. Azathioprine/mercaptopurine or mesalamine (more than 3 g/day) can also be used after surgical resection to prevent recurrence.
   d. Infliximab 5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks or adalimumab 40 mg subcutaneously every other week (starting on day 29 of therapy)
   e. Vedolizumab 300 mg (or natalizumab) intravenously every 4 weeks can be considered for patients who did not respond to conventional medical therapy.
   f. Ustekinumab 90 mg subcutaneously every 8 weeks can be used for patients whose conventional or TNF inhibitor therapy has failed.
   g. Methotrexate intramuscularly 25 mg for up to 16 weeks, followed by 15 mg/week intramuscularly, is effective for patients with chronic active disease.
6. Perianal disease
   a. Simple perianal fistulas (a single tract without abscess and involving less than 30% of the external sphincter; better prognosis; can be treated less aggressively than complex fistulas)
      i. Antibiotics: metronidazole or ciprofloxacin
      ii. Azathioprine/mercaptopurine
      iii. Infliximab, adalimumab, certolizumab
   b. Complex perianal fistulas (involving more than 30% of the external sphincter, multiple tracts, abscess involvement, recurrent fistulas, rectovaginal fistulas; worse prognosis requiring more aggressive therapy than simple fistulas.)
      i. Infliximab, adalimumab, or certolizumab in combination with surgery
      ii. Antibiotics: Metronidazole or ciprofloxacin (mainly as adjunctive therapy in this case)
      iii. Azathioprine/mercaptopurine or methotrexate

Patient Cases

4. A 35-year-old man presents with newly diagnosed mildly active UC affecting his descending colon and rectum (left-sided disease). He takes loratadine 10 mg/day for seasonal allergies. He has no known drug allergies. Which drug regimen is best?
   A. Balsalazide 750 mg twice daily.
   B. Methotrexate 25 mg intramuscularly once weekly.
   C. Infliximab 5 mg/kg intravenously.
   D. Mesalamine enema 4000 mg rectally once daily.

5. A 25-year-old woman (height 65 inches, weight 54.4 kg) presents to the clinic with a 12-week history of cramping abdominal pain, fever, fatigue, and 3 or 4 bloody stools per day. A colonoscopy reveals patchy inflammation in the colon and terminal ileum consistent with moderately active CD. She has an allergy to penicillin (rash). Vital signs include body temperature 98°F, heart rate 100 beats/minute, respiratory rate 18 breaths/minute, and blood pressure 118/68 mm Hg. Which therapeutic choice is best?
   A. Mesalamine (Pentasa) 1000 mg four times daily.
   B. Infliximab (Remicade) 275 mg intravenously and azathioprine 110 mg daily.
   C. Budesonide (Entocort) 9 mg orally once daily.
   D. Adalimumab (Humira) 40 mg subcutaneously every 2 weeks.

V. COMPLICATIONS OF LIVER DISEASE

A. Severity of liver disease is assessed using scoring tools such as the Chuld-Turcotte-Pugh or model for end-stage liver disease (MELD) scores (Tables 12 and 13).

Table 12. Child-Turcotte-Pugh Classification of the Severity of Cirrhosis

Variable	Score		
	1 Point	2 Points	3 Points
Encephalopathy	Absent	Mild-moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds above normal)	1–4	4–6	>6

[a]Class A = total score of 5 or 6; class B = total score of 7–9; class C = total score of 10 or more.

Table 13. Model for End-Stage Liver Disease (MELD)

Version	Calculation	Comments
Original	9.57 × ln(creatinine) + 3.78 × ln(total bilirubin) + 11.2 × ln(INR) + 6.43	Score ranges from 6 to 40 Higher number indicates more severe disease Used to predict mortality and prioritize patients for liver transplantation
MELD-Na	MELD − Na − [0.025 × MELD × (140 − Na)] + 140	Incorporates sodium May better discriminate risk of death
UNOS modification	Original MELD equation with limits set on laboratory values that are entered	Lower end of laboratory values for SCr, bilirubin, and INR are set at 1 with a maximum of 4 If two or more dialysis treatments within the prior week or within 24 hr of CVVHD within the prior week, SCr concentration automatically set to 4.0 mg/dL

CVVHD = continuous venovenous hemodialysis; INR = international normalized ratio; MELD = model for end-stage liver disease; Na = sodium, UNOS = United Network for Organ Sharing.

B. Ascites
   1. Definition: Free fluid in the abdominal cavity owing to increased resistance within the liver (forces lymphatic drainage into the abdominal cavity) and reduced osmotic pressure within the bloodstream (hypoalbuminemia); develops at a 5-year cumulative rate of 30% in compensated liver disease
   2. Clinical features: protuberant abdomen, shifting dullness, fluid wave, bulging flanks, abdominal pain
   3. Diagnosis
      a. Clinical features
      b. Abdominal ultrasonography
      c. Paracentesis, use to determine serum-ascites albumin gradient (SAAG), calculated by subtracting the ascites albumin concentration from the serum albumin concentration; a value greater than 1.1 indicates ascites caused by portal hypertension
   4. Treatment
      a. Alcohol cessation if alcohol induced. Reduce alcohol consumption to mild amounts in non-alcoholic fatty liver disease.
      b. Attainment of negative sodium balance
         i. Dietary sodium restriction (<2000 mg/day), fluid restriction (<1.5 L/day) if serum sodium is less than 120–125 mmol/L
         ii. Goal is sodium excretion greater than 78 mmol/day. A random spot urine sodium concentration greater than the potassium concentration (ratio greater than 1) correlates with a 24-hour sodium excretion of greater than 78 mmol/day with 90% accuracy.
         iii. Diuretics
            (a) Combination furosemide and spironolactone is preferred initial therapy in most patients. A ratio of 40 mg of furosemide to 100 mg of spironolactone is an appropriate starting regimen. Amiloride 10–40 mg/day can be substituted for spironolactone in patients who develop tender gynecomastia. Other loop diuretics may be used in place of furosemide, though they may be associated with additional cost.
            (b) If tense ascites is present, large-volume paracentesis can be used. Administer albumin at a dose of 6–8 g/L of ascitic fluid removed if more than 5 L is removed at one time.
            (c) If refractory ascites is present, consider midodrine 7.5 mg three times daily as add-on therapy to diuretics.

iv. No upper limit of weight loss if massive edema is present, 0.5 kg/day in patients without edema
v. Monitor for electrolyte imbalances, renal impairment, and gynecomastia (spironolactone).

c. Discontinue drugs associated with sodium/water retention, such as NSAIDs. Avoid angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to prevent renal failure.

C. Hepatic encephalopathy

1. Definition: Hepatic encephalopathy is brain dysfunction caused by liver insufficiency or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.
   a. Thought to be secondary to the accumulation of nitrogenous substances (mainly NH_3) arising from the gut. Overall, NH_3 serum concentrations do not correlate well with mental status
   b. Other theories are related to the activation of γ-aminobutyric acid receptors by endogenous benzodiazepine-like substances, possible zinc deficiency, or altered cerebral metabolism.
2. Clinical features and criteria
   a. Can result in acute encephalopathy with altered mental status and progress to coma if untreated; asterixis ("hand flap") is a classic physical finding
   b. May be precipitated by various factors including constipation, GI bleeding, infection, hypokalemia, dehydration, hypotension, and CNS-active drugs (benzodiazepines and narcotics)
   c. The West Haven Criteria and the Glasgow Coma Scale are used to classify and grade; see Table 14.

Table 14. Common Criteria and Clinical Symptoms for Hepatic Encephalopathy

West Haven Criteria	ISHEN	Clinical Description
Unimpaired		No current or history of encephalopathy
Minimal	Covert	Psychometric or neuropsychologic alterations of tests exploring psychomotor speed and executive functions or neurophysiologic alterations without clinical evidence of mental change
Grade I		Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction Altered sleep rhythm
Grade II	Overt	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis
Grade III		Somnolence to semistupor Responsive to stimuli Confused Gross disorientation Bizarre behavior
Grade IV		Coma

ISHEN = International Society for Hepatic Encephalopathy and Nitrogen Metabolism.

3. Classifications
   a. Subtypes according to underlying disease
      i. Type A: Owing to acute liver failure
      ii. Type B: Owing to portosystemic bypass or shunting
      iii. Type C: Owing to cirrhosis
   b. Duration
      i. Episodic
      ii. Recurrent (occurs within a time frame of 6 months or less)
      iii. Persistent: Denotes a pattern of behavioral alteration that is always present and interspersed with relapses of overt hepatic encephalopathy
   c. Presence or absence of precipitating factors
4. Treatment
   a. Assess need for airway support and remove possible precipitating factors.
   b. Main treatments targeted at reducing the nitrogen load in the gut.
   c. Treatment recommendations are based on type C (Table 15).

Table 15. Treatment of Hepatic Encephalopathy Owing to Cirrhosis (Type C)

Type	Recommendations
Episodic overt HE (type C)	Treat episodic overt HE and then use secondary prophylaxis
	Primary prophylaxis is not indicated unless cirrhosis and high risk for HE
	Lactulose is first-line treatment for overt HE
	Rifaximin can be used as add-on therapy with lactulose to prevent recurrence after the second episode of overt HE
	Oral BCAA or IV LOLA can be used as alternative or additional therapy in patients unresponsive to traditional therapies
	Neomycin or metronidazole can be used as alternative treatment

BCAA = branched chain amino acids; HE = hepatic encephalopathy; IV = intravenous; LOLA = L-ornithine L-aspartate.

   d. Lactulose
      i. Nonabsorbable disaccharide: Metabolized by colonic bacteria to acetic and lactic acid. NH_3 present in the GI lumen is reduced to ammonium ion (NH_4^+) through the reduction in pH ("ammonia trapping") and is unable to diffuse into the bloodstream. Lactulose can also alter bacterial metabolism, resulting in increased uptake of NH_3.
      ii. Dose: 45 mL orally every 1–2 hours until the patient has a loose bowel movement and then titrate to two or three loose bowel movements per day (typically, 15 to 45 mL two or three times daily); may also administer as an enema (300 mL plus 700 mL of water retained for 1 hour). Powder formulation (Kristalose) is available in 10- and 20-g packets to be dissolved in 120 mL water (10 g = 15 mL traditional lactulose). This formulation is more palatable than traditional syrup.
      iii. Can be continued long term to prevent recurrent encephalopathy
      iv. Flatulence, diarrhea, and abdominal cramping are common adverse effects.
   e. Antibiotics
      i. Targeted at reducing the number of intraluminal urease-producing bacteria that can lead to excess NH_3 production
      ii. Neomycin (3–6 g/day in three or four divided doses for 1–2 weeks and then 1–2 g/day maintenance) or metronidazole (250 mg orally twice daily) can be used; neomycin is considered as effective as lactulose.

iii. From 1% to 3% of neomycin is absorbed. Caution is required for with long-term use with renal insufficiency. Long-term metronidazole can result in peripheral neuropathy.
iv. Rifaximin is as effective as lactulose and other nonabsorbable antibiotics, and it may be better tolerated. The approved dose for reduction in overt encephalopathy in patients 18 years and older is 550 mg twice daily. Drug cost may be greater, but this may be offset by fewer hospitalizations and shorter lengths of stay. Previous studies in the short-term setting have used 400 mg three times daily.

f. Other possible treatments
i. Polyethylene glycol 3350 4 L given orally or by nasogastric tube over 4 hours resulted in faster improvement in encephalopathy than lactulose.
ii. Benzodiazepine antagonists such as flumazenil can be used in cases of possible benzodiazepine overdose; however, the risk of lowering the seizure threshold often limits their use.
iii. Zinc supplementation should be used in patients with documented zinc deficiency.
iv. Branched-chain amino acids and intravenous L-ornithine L-aspartate are alternative or additional therapies in patients who are unresponsive to traditional therapies
v. Nutritional interventions include 35–40 kcal/kg/day based on IBW and 1.2–1.5 g/kg/day protein intake

D. Gastroesophageal varices
1. Background
a. Resistance to blood flow within the liver caused by cirrhosis results in portal hypertension. Collateral blood vessels (e.g., esophageal varices) are formed because of this increased resistance to blood flow.
b. Variceal hemorrhage can occur in 25%–35% of patients with cirrhosis and varices; mortality rates are as high as 30%–50% per bleed; recurrence rates are as high as 70% within the first 6 months after an initial bleed.
2. Management of acute variceal bleeding
a. Fluid resuscitation and hemodynamic stabilization. Maintain hemoglobin concentration of about 8 g/dL. Administration of fresh frozen plasma or platelets can be considered for patients with considerable coagulopathy.
b. Endoscopy to provide assessment and possible intervention
i. Sclerotherapy stops bleeding in 80%–90% of patients; it may be associated with complications such as perforation, ulceration, stricture, and bacteremia. Possible sclerosing agents are ethanolamine and sodium tetradecyl sulfate.
ii. Endoscopic variceal band ligation can be used as an alternative to sclerotherapy, with fewer complications.
c. Medical management of acute variceal bleeding
i. Institute after fluid resuscitation (before endoscopy, if possible)
ii. Most therapies are targeted at reducing splanchnic blood flow and portal pressure; a combination of endoscopic and vasoactive therapies is most effective.
iii. Somatostatin analog: Octreotide
(a) Prevents postprandial hyperemia by reducing portal pressure (by reduced splanchnic blood flow) through inhibitory effects on vasoactive peptides such as glucagon, or by a local vasoconstrictor effect
(b) Preferred agent in combination with endoscopic interventions because of more favorable adverse effect profiles; main adverse effects include hyperglycemia and abdominal cramping
(c) Dosing: 50-mcg intravenous bolus, then 50 mcg/hour intravenously for 3–5 days

iv. Vasopressin: 0.2–0.4 unit/minute plus nitroglycerin 40–400 mcg/minute for 3–5 days
  (a) Vasopressin use results in splanchnic vasoconstriction; it is used less often secondary to the need for both drugs and coronary vasoconstriction/ hypertension with vasopressin (nitroglycerin attenuates these effects to some extent).
  (b) Vasopressin has a worse adverse effect profile than octreotide. Risk of ischemia, hypotension, and skin necrosis limit use.

v. Nondrug measures to control bleeding
  (a) Typically used for medically unresponsive bleeding
  (b) Minnesota or Blakemore tube: Balloon compression applied directly to bleeding varices
  (c) Transjugular intrahepatic portosystemic shunt results in shunting of blood from the portal circulation; this may be associated with complications such as bleeding, infection, and increased risk of hepatic encephalopathy
  (d) Surgery

vi. Antibiotic therapy
  (a) The use of oral or intravenous prophylactic antibiotics in patients with cirrhosis with variceal bleeding reduces short-term mortality; these agents should be prescribed.
  (b) Typical regimens include ceftriaxone intravenously 1 gram/day for 7 days, especially when quinolone-resistant bacteria are prevalent or the patient has been receiving quinolone prophylaxis. Fluoroquinolone can be considered in patients who do not have a high risk of quinolone resistance.

d. Prevention of variceal bleeding

i. Primary prophylaxis
  (a) A screening esophagogastroduodenoscopy is recommended to evaluate for esophageal and gastric varices when the diagnosis of cirrhosis is made.
  (b) Pharmacologic therapy is not recommended to prevent the development of varices in patients with cirrhosis who have not yet developed varices.
  (c) Patients who have small varices and no history of bleeding, but meet the criteria for increased risk of bleeding (Child-Pugh class B or C, red wale marks on varices), should receive preventive drug therapy with nonselective β-blockers.
  (d) Nonselective β-blockers can be considered; however, the long-term benefit is unclear in patients who have small varices and no history of bleeding, but who do not meet the criteria for increased risk of bleeding.
  (e) Nonselective β-blockers are indicated in all patients with medium or large varices and no history of bleeding. An endoscopic variceal ligation (EVL) can be used if nonselective β-blockers are contraindicated.
  (f) Mechanism of nonselective β-blockers: Blockade of β_1-receptors reduces cardiac output, whereas blockade of β_2-receptors prevents splanchnic vasodilation; unopposed α_1-mediated constriction of the splanchnic circulation also leads to reductions in portal pressure.
  (g) Therapy should aim for a resting heart rate of 55–60 beats/minute or a 25% reduction from baseline.
  (h) Nonselective β-blockers (propranolol, nadolol, carvedilol) are associated with a significant reduction in the incidence of first bleed.
  (i) Long-acting nitrates (isosorbide mononitrate or dinitrate) should not be used for primary prophylaxis. These agents are believed to decrease intrahepatic resistance and are considered as effective as propranolol; however, there is an increased incidence of mortality in some studies when they are used as monotherapy.
  (j) Shunt surgery or endoscopic sclerotherapy should not be used for primary prophylaxis.

ii. Secondary prophylaxis
   (a) All patients with a history of variceal bleeding should receive secondary prophylaxis to prevent recurrent bleeding.
   (b) A combination of endoscopic variceal band ligation and nonselective β-blockers is considered the most effective regimen.
   (c) Nonselective β-blockers are associated with approximately a 20% reduction in the incidence of variceal rebleeding; reductions in mortality are minimal and inconsistent between trials. Most studies are of patients with Child-Turcotte-Pugh class A or B cirrhosis; class C patients may be unable to tolerate β-blockers.
   (d) Combining nonselective β-blockers with nitrates leads to slightly higher reductions in rebleeding rates; no added mortality benefit is observed, and there is a higher incidence of adverse effects with the combination.
   (e) Sclerotherapy is no longer recommended for secondary prophylaxis because EVL has been shown to be better, with fewer complications.
   (f) The transjugular intrahepatic portosystemic shunt is highly effective at preventing recurrent bleeding; however, it is associated with a 30%–40% incidence of encephalopathy and is reserved for medically unresponsive patients.
   (g) Contraindications to nonselective β-blockers: asthma, insulin-dependent diabetes with frequent hypoglycemia, peripheral vascular disease
   (h) Adverse effects of nonselective β-blockers: light-headedness, fatigue, shortness of breath, sexual dysfunction, bradycardia
   (i) Adverse effects of EVL: transient dysphagia, chest discomfort

E. Spontaneous bacterial peritonitis (SBP)
   1. Background
      a. Definition: SBP is the infection of previously sterile ascitic fluid without an apparent intra-abdominal source; it is considered primary, as opposed to secondary, peritonitis.
      b. May be present in 10%–30% of hospitalized patients with cirrhosis and ascites
      c. Associated with 20%–40% of in-hospital mortality; poor prognosis after recovery, with 2-year survival after initial episode reported at about 30%
   2. Pathophysiology
      a. Principal theory is seeding of the ascitic fluid from an episode of bacteremia.
      b. The bacteria present are usually enteric pathogens; thus, they may enter the blood because of increases in gut permeability secondary to portal hypertension, suppression of hepatic reticuloendothelial cells, or translocation of the gut wall and dissemination through the mesenteric lymph system.
      c. Reduced opsonic activity of the ascitic fluid and alterations in neutrophil function may also be contributing factors.
      d. Enteric gram-negative pathogens are most commonly involved, and more than 90% of cases involve a single bacterial species. (Table 16)

Table 16. Most Commonly Isolated Bacteria Responsible for Spontaneous Bacterial Peritonitis

Gram-negative Bacilli (50%)	Gram-positive Bacilli (17%)
Escherichia coli, 37%	*Streptococcus pneumoniae*, 10%
Klebsiella spp., 6%	Other streptococci, 6%
Other, 7%	*Staphylococcus aureus*, 1%

3. Clinical and laboratory features
    a. Clinical presentation can vary. Common symptoms include fever, abdominal pain, nausea, vomiting, diarrhea, rebound tenderness, and exacerbation of encephalopathy. About 33% of patients present with renal failure, which is associated with significant increases in mortality. GI bleeding and septic shock or hypotension rarely occur.
    b. Laboratory
        i. May see systemic leucocytosis or increases in SCr
        ii. Abdominal paracentesis must be performed
            (a) The presence of more than 250 polymorphonuclear cells/mm^3 is diagnostic for SBP.
            (b) Lactate dehydrogenase, glucose, and protein values may help to distinguish it from secondary peritonitis.
        iii. Blood culture results are positive in 50%–70% of cases; ascitic fluid culture results positive in 67% of cases.
        iv. Gram stain of ascitic fluid is typically low yield.
4. Treatment of acute SBP
    a. Because of the high associated mortality, treatment should be initiated promptly in patients with clinical and laboratory features consistent with SBP. If there are fewer than 250 cells/mm^3 ascitic fluid polymorphonuclear cells, empiric antibiotic therapy can be initiated if other signs of infection are present.
    b. Up to 86% of ascitic fluid culture results may be negative if one dose of an antibiotic is given before cultures are obtained.
    c. Predictors of poor outcomes include bilirubin greater than 8 mg/dL, albumin less than 2.5 g/dL, creatinine greater than 2.1 mg/dL, hepatic encephalopathy, hepatorenal syndrome, and upper GI bleeding.
    d. Antibiotic therapy plus albumin if patient meets criteria for use (see below)
        i. Empiric therapy targeting enteric gram-negative organisms should be instituted.
        ii. Third-generation intravenous cephalosporins have been studied the most and are considered first line: cefotaxime (2 g every 8–12 hours) or ceftriaxone (2 g/day)
        iii. Other agents, such as fluoroquinolones, can be used. Ofloxacin 400 mg orally twice daily can be considered in patients without prior exposure to fluoroquinolones and no evidence of shock, vomiting, grade II or higher encephalopathy, or SCr greater than 3 mg/dL.
        iv. Avoid aminoglycosides because of the high risk of renal failure in patients with cirrhosis and SBP.
        v. Treatment duration: 5–10 days; most studies suggest that 5-day treatment is as effective as 10-days.
    e. Albumin
        i. Rationale: The hemodynamics of patients with cirrhosis reflect a state of intravascular hypovolemia and organ hypoperfusion; SBP is thought to exacerbate this effect, resulting in progressive renal hypoperfusion and precipitation of renal failure or hepatorenal syndrome.
        ii. The regimen most commonly used is based on one study (N Engl J Med 1999;341:403-9).
            (a) Albumin dosing: 1.5 g/kg on admission; 1 g/kg on hospital day 3
            (b) In addition, give antibiotic treatment; cefotaxime was used in this study.
            (c) The incidence of renal failure was 10%, versus 33% for placebo (p=0.002).
            (d) In-hospital mortality was 10% for albumin, 29% for placebo (p=0.01).
            (e) Thirty-day mortality was 21% with albumin, versus 41% for placebo (p=0.03).
            (f) Guidelines suggest using this albumin regimen with antibiotics if SCr > 1 mg/dL, BUN > 30 mg/dL, or total bilirubin > 4 mg/dL.

5. Prevention
    a. Prophylactic oral antibiotics are used to reduce the number of enteric organisms in the GI tract (GI decontamination), with the hope of reducing the chance of bacterial translocation to prevent SBP in high-risk patients.
    b. Antibiotic regimens are similar for both primary and secondary prevention:
        i. Fluoroquinolones: ciprofloxacin or norfloxacin (not available in the United States)
        ii. Trimethoprim/sulfamethoxazole 1 double-strength tablet for 5 consecutive days per week
    c. Primary prevention
        i. During acute upper GI bleeding, give 7-day course of ceftriaxone during hospitalization.
        ii. Can also consider indefinite antibiotic prophylaxis in patients without GI bleeding if ascitic fluid protein concentration is less than 1.5 g/dL and at least one of the following is present: SCr > 1.2 mg/dL, BUN > 25 mg/dL, sodium < 130 mg/dL, or Child-Turcotte-Pugh score > 9 with bilirubin > 3 mg/dL
        iii. Use norfloxacin 400 mg once daily or trimethoprim/sulfamethoxazole.
    d. Secondary prevention
        i. All patients recovering from an initial episode of SBP should be treated with oral prophylactic antibiotics indefinitely.
        ii. Consider patient for liver transplantation because 2-year survival is 25%–30% after recovery.

F. Hepatorenal syndrome
1. Criteria in patients with cirrhosis and ascites: SCr > 1.5 mg/dL, no improvement in SCr to less than 1.5 mg/dL after withdrawal of diuretics and administration of albumin, absence of shock, no current nephrotoxins, absence of parenchymal kidney disease and microhematuria, and a normal renal ultrasound
2. Subtypes
    a. Type 1: Doubling of SCr to greater than 2.5 mg/dL or a 50% reduction in creatinine clearance (CrCl) to less than 20 mL/minute/1.73 m^2 in less than 2 weeks
    b. Type 2: Nonrapid progression of worsening of renal function. Associated with high mortality.
3. Treatment: Albumin in combination with octreotide (200 mcg subcutaneously three times daily) or midodrine (12.5 mg three times daily maximum) may be considered for type 1 hepatorenal syndrome. Albumin plus norepinephrine may be considered if the patient is in the intensive care unit.

G. Alcoholic liver disease
1. Subset of chronic liver disease. Patients may develop steatosis and eventually progress to cirrhosis. About 10%–35% of patients may develop severe alcoholic hepatitis.
2. Prognosis of alcoholic hepatitis may be initially evaluated by the Maddrey discriminant function (MDF) score, calculated as 4.6 × (Patient's PT − Control PT) + Total bilirubin (mg/dL), where PT is prothrombin time. Patients whose score is greater than 32 have a poor prognosis. Patients with a MELD score greater than 20 should also be considered for drug therapy.
    a. Patients with an MDF greater than 32, with or without encephalopathy, or a MELD score greater than 20 should be considered for a 4-week course of prednisolone 40 mg/day, followed by a 2-week taper. This may lead to a 30% decrease in the risk ratio of short-term death. A Lille score calculation, which is a dynamic measure that considers the change in bilirubin, should be assessed after 7 days of corticosteroid therapy to determine whether improved laboratory findings warrant continuation of the corticosteroid course for the full 28 days.
    b. Intravenous acetylcysteine in combination with corticosteroids should be considered depending on survival benefit and reduction in early complications (infection, hepatorenal syndrome) compared with corticosteroid therapy alone.
    c. Pentoxifylline therapy is no longer recommended for alcoholic hepatitis.

Patient Cases

6. A 47-year-old woman with a history of alcoholic cirrhosis (Child-Turcotte-Pugh class C) is admitted to the hospital with nausea, abdominal pain, and fever. Physical examination reveals a distended abdomen with shifting dullness, a positive fluid wave, and the presence of diffuse rebound tenderness. She also has 1+ lower extremity edema. Current medications include furosemide 80 mg twice daily and spironolactone 200 mg once daily. A diagnostic paracentesis reveals turbid ascitic fluid, which was sent for culture. Laboratory analysis of the fluid revealed an albumin concentration of 0.9 g/dL and the presence of 1×10^3 white blood cells (45% polymorphonuclear neutrophils). Serum laboratory studies reveal SCr 1.2 mg/dL, BUN 37 mg/dL, AST 60 IU/mL, ALT 20 IU/mL, serum albumin 2.5 g/dL, and total bilirubin 3.2 mg/dL. What is the best course of action?
   A. Initiate intravenous albumin and await culture results.
   B. Initiate intravenous vancomycin plus tobramycin.
   C. Initiate intravenous cefotaxime plus albumin therapy.
   D. Initiate oral trimethoprim/sulfamethoxazole double strength.

7. A 56-year-old man with a history of Child-Turcotte-Pugh class B cirrhosis secondary to alcohol abuse is admitted with a 2-day history of confusion, disorientation, somnolence, and reduced oral intake. On examination, he is afebrile, with abdominal tenderness, reduced reflexes, dry mucous membranes, and asterixis. Paracentesis is negative for infection. He takes propranolol 40 mg three times daily. Which recommendation is best for treating this patient's hepatic encephalopathy?
   A. Initiate rifaximin 550 mg orally twice daily.
   B. Initiate lactulose 30 mL orally every 2 hours.
   C. Initiate polyethylene glycol 3350 17 g orally twice daily.
   D. Initiate ceftriaxone 1 g intravenously daily.

VI. VIRAL HEPATITIS

A. Definitions: For all hepatitis virus infections, acute hepatitis is defined as infection for less than 6 months, whereas chronic infection is infection for more than 6 months.

B. HAV
   1. Background
      a. An RNA virus that is associated with the development of self-limited hepatitis
      b. Transmission occurs mainly through the fecal–oral route.
         i. Areas of poor sanitation; also flooding leading to increased spread
         ii. Foodborne: shellfish, water, milk, vegetables
         iii. Person-to-person contact: sexual, day care, intravenous drug use, household, restaurant workers
      c. After exposure, incubation for 14–50 days occurs; patients may have general, nonspecific symptoms such as nausea, vomiting, diarrhea, myalgia, fever, abdominal pain, and jaundice.
      d. Most patients have self-limited disease lasting less than 2 months; death of the hepatocyte results in elimination of the virus.
      e. HAV is associated with very low mortality (less than 1%) and is not associated with the development of chronic hepatitis. Fulminant hepatitis can occur in some instances.

2. Diagnosis
    a. Clinical signs and symptoms include nausea, abdominal pain, jaundice, fever, malaise, or anorexia. Some patients may have mild asymptomatic disease.
    b. Recent possible exposures
    c. Laboratory data
        i. IgM antibody to HAV (anti-HAV) is detectable in the serum 5–10 days before the onset of symptoms. Once the infection clears, the IgM antibody is replaced by IgG antibodies during a 2- to 6-month period. These antibodies confer lifelong protective immunity against subsequent infection.
        ii. Elevation of aminotransferases
    d. Management of acute HAV infection is mainly supportive; avoid hepatotoxic medications, such as acetaminophen.
3. Preexposure prophylaxis
    a. Active (vaccination) or passive (immune globulin) prophylaxis can be used.
    b. Havrix (GlaxoSmithKline) and Vaqta (Merck) are the two available HAV vaccines; Twinrix is a combination HAV and HBV product (GlaxoSmithKline).
    c. Populations requiring preexposure prophylaxis with HAV vaccine
        i. All children older than 1 year
        ii. Homelessness
        iii. People working in or traveling to countries with high or intermediate endemicity (may take up to 4 weeks for full protection)
        iv. Men who have sex with men
        v. Injection or non-injection drug users
        vi. Those who work with hepatitis A virus in research laboratories
        vii. Patients with chronic liver disease
        viii. Patients with clotting factor disorders
        ix. Close, personal contact with international adoptee
    d. Populations requiring preexposure prophylaxis with HAV immune globulin
        i. Travelers to endemic countries
        ii. Children younger than 1 year (vaccine not approved for this age group)
        iii. Doses: 0.1 mL/kg for travel up to 1 month, 0.2 mL/kg for travel up to 2 months, 0.2 mL/kg every 2 months for travel longer than 2 months. Administer intramuscularly.
4. Postexposure prophylaxis
    a. Immune globulin can be given at a dose of 0.1 mL/kg intramuscularly within 2 weeks of exposure. HAV vaccine is recommended in patients 12 months to 40 years old who are otherwise healthy. Patients older than 40 should receive the vaccine with or without concurrent immune globulin administration. Patients 12 months and older who are immunocompromised or who have chronic liver disease should receive both the vaccine and immune globulin.
    b. Offer to those not previously vaccinated in the following situations:
        i. Close personal contact with a documented infected person
        ii. Staff or attendees of day care centers if one or more cases are recognized in children or employees or if cases are recognized in two or more households of attendees
        iii. Common source of exposures
            (a) If a food handler receives a diagnosis of HAV, vaccine or immune globulin should be administered to other food handlers at the same establishment. Administration of HAV vaccine or immune globulin to patrons typically is not indicated, but may be considered if:
                (1) The food handler was probably infectious, and he or she both directly handled uncooked or cooked food and had diarrhea or poor hygienic practices.
                (2) Patrons can be identified and treated in 2 weeks or less after exposure.

(b) In settings where repeated exposures to HAV might have occurred, stronger consideration of HAV vaccine or immune globulin use could be warranted. In a common-source outbreak, postexposure prophylaxis should not be provided to exposed individuals after cases have begun to occur, because the 2-week period after exposure during which immune globulin or HAV vaccine is known to be effective will have been exceeded.

C. HBV
1. Background
   a. HBV is a DNA virus; there are more than 350 million infected patients worldwide.
   b. Transmission routes
      i. Parenteral: intravenous drug abuse, needlestick, transfusion, ear or body piercing
      ii. Bodily fluids: saliva, semen, vaginal fluid
      iii. Sexual contact: heterosexual and homosexual
      iv. Perinatal: mother to child at birth
   c. Associated with both acute and chronic disease. Natural history of HBV is age dependent. Risk of developing chronic infection after an acute infection is 90% in neonates, 25%–30% in children younger than 5 years, and 10% in adults.
   d. Chronic infection with HBV increases the risk of hepatocellular carcinoma.
   e. Diagnosis
      i. Clinical signs and symptoms: nausea, vomiting, diarrhea, myalgia, fever, abdominal pain, jaundice (30% may have no symptoms)
      ii. Serologic diagnosis (Table 17)
      iii. Combinations of serologic markers must be reviewed to distinguish acute from chronic infections.
      iv. Eight different HBV genotypes (A–H) exist. Routine genotype testing is not endorsed by the guidelines.

Table 17. HBV Serologies

Serologic Marker	Abbreviation	Comment
Surface antigen	HBsAg	First detectable serum antigen during acute infection; also present in chronic infection
Core antigen	HBcAg	Present early after cell damage during acute infection; typically cannot measure this in the serum
E antigen	HBeAg	Denotes ongoing active viral replication
Anti–surface antigen antibody	Anti-HBs	Confers protective immunity; present after recovery from acute infection or after vaccination
Anticore antigen antibody (IgG)	Anti-HBc	Appears at onset of symptoms Denotes prior exposure to HBV Cannot use to distinguish acute from chronic infection
Anti-E antibody	Anti-HBe	May indicate peak replication has passed
HBV DNA	HBV DNA	Marker of active HBV replication

HBcAg = hepatitis B core antigen; HBeAg = hepatitis B early antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; Ig = immunoglobulin.

(a) Most patients have hepatitis B envelope antigen (HBeAg)-positive disease.
(b) HBeAg-negative disease: Mutation in the precore or core promoter regions. These variants are known as precore mutants; these mutations do not allow monitoring of loss of E antigen as a clinical marker of suppressed replication. Monitor reduction in HBV DNA; patients infected with these variants also tend to have lower serum HBV DNA and fluctuating liver function tests.
(c) Centers for Disease Control and Prevention guidelines for screening for HBV infection indicate that the serologic assay for HBV surface antigen (HBsAg) should be the serologic screening test used for the following populations. Additional HBV tests are needed in combination with the HBsAg for select populations as listed below.
    (1) People born in geographic regions with HBsAg prevalence greater than 2% regardless of vaccination history
    (2) Men who have sex with men; also test for anti-HBc or anti-HBs
    (3) Past or current intravenous drug users; also test for anti-HBc or anti-HBs
    (4) Patients receiving cytotoxic chemotherapy or immunosuppressive therapy related to organ transplantation or rheumatologic or GI disorders. In addition, test for anti-HBc or anti-HBs.
    (5) U.S.-born people not vaccinated as infants whose parents were born in regions with HBV endemicity greater than 8%
    (6) People with elevated ALT and AST of unknown etiology
    (7) Donors of blood, plasma, organs, tissues, or semen. In addition, test for anti-HBc and HBV DNA.
    (8) Pregnant women (during each pregnancy, preferably in the first trimester)
    (9) Infants born to HBsAg-positive mothers
    (10) Household, needle sharing, or sex contacts of people known to be HBsAg positive. In addition, test for anti-HBc or anti-HBs.
    (11) People who are the sources of blood or bodily fluid for exposures that might require postexposure prophylaxis
    (12) People who are HIV positive. In addition, test for anti-HBc or anti-HBs.

v. Clinical definitions (Table 18)

Table 18. Clinical Definitions of HBV

Chronic HBV Infection	Inactive HBV Carrier State
HBsAg positive > 6 mo Serum HBV DNA 20,000 IU/mL (105 copies/mL), lower values 2000–20,000 IU/ mL (104–105 copies/mL) are often observed in HBeAg-negative chronic HBV Persistent/intermittent elevation of AST and ALT Chronic hepatitis and moderate-severe necroinflammation on biopsy	HBsAg positive > 6 mo HBeAg negative, anti-HBeAg positive Serum HBV DNA < 2000 IU/mL (104 copies/mL) Persistently normal AST and ALT; absence of significant hepatitis on biopsy

ALT = alanine aminotransferase; AST = aspartate aminotransferase

2. Treatment of chronic infection
    a. Treatment recommendations
        i. Patients who are HBeAg positive with elevated ALT concentrations and compensated liver disease should be observed for 3−6 months for spontaneous conversion from HBeAg positive to anti-HBe (or HBeAb positive) indicating seroconversion, before initiating treatment. Antiviral treatment should be considered in patients whose ALT remains greater than 2-fold the ULN and whose HBV DNA is greater than 20,000 IU/mL.
        ii. Patients who are HBeAg negative with positive anti-HBe, normal ALT, and HBV < 2000 IU/mL should be monitored every 3 months for 1 year and then every 6–12 months if they remain in the inactive carrier state.
    b. Patients who meet the criteria for chronic infection should be treated. Choice of initial therapy is based on patient profile, prior treatments, contraindications to drug therapy, and medication and monitoring costs.
    c. Monitoring for efficacy should be based on the following responses:
        i. Biochemical: Reduction of liver function tests to within the normal range
        ii. Virologic: Reduction of HBV DNA to undetectable concentrations and loss of HBeAg if HBeAg positive
            (a) A primary nonresponse is considered a decrease in HBV DNA of less than 2 log/mL after at least 24 weeks of therapy. Patients who do not meet these criteria should receive an alternative treatment.
            (b) Response should be assessed by reductions in HBV DNA for HBeAg-negative patients.
3. Drug therapies
    a. Pegylated interferon
        i. Cytokine with antiviral, antiproliferative, and immunomodulatory effects
        ii. Best predictors of response to treatment are high pretreatment ALT, low-serum HBV DNA, presence of active inflammation on biopsy, and acquisition of infection; adult HBeAg-negative disease responds less favorably to interferon.
        iii. Dosing
            (a) Pegylated interferon is recommended over interferon alfa because of its reduced dosing frequency and improved tolerance.
            (b) Pegylated-α-2a (Pegasys): 180 mcg subcutaneously once weekly for 48 weeks (duration is the same for HBeAg-negative and HBeAg-positive disease)
        iv. If a response is obtained, it is usually long lasting (more than 4 years).
        vi. Treatment with interferon typically results in an increase in ALT 4–8 weeks into treatment. This response is expected; it should not be viewed as an adverse effect of therapy.
        vii. Adverse effects
            (a) Interferon is associated with many serious adverse effects, including bone marrow suppression.
                (1) Leukopenia: May use filgrastim (granulocyte colony-stimulating factor) for support. Requires frequent monitoring of complete blood cell count (every 1–3 months)
                (2) Thrombocytopenia: Minimal data with oprelvekin (interleukin-11). Not used because of many adverse effects including pulmonary hypertension
            (b) Predisposition to infections
            (c) CNS: depression, psychosis, anxiety, insomnia, seizures. Adverse CNS effects occur in 22%–31% of patients.
            (d) Flulike symptoms (tolerance usually develops after a few weeks)
            (e) Anorexia, alopecia, thyroid dysfunction, neuropathy

(f) Exacerbation of underlying autoimmune disorders (i.e., thyroid). Thyroid-stimulating hormone testing recommended every 3 months
(g) Ischemic or hemorrhagic cerebrovascular disorders
(h) Serious hypersensitivity and rash formation
(i) Manufacturers give recommendations for dose reductions in patients who develop bone marrow suppression and depression while on therapy.
(j) Contraindicated in patients with current psychosis, a history of severe depression, neutropenia, thrombocytopenia, symptomatic heart disease, decompensated liver disease, and uncontrolled seizures; also use caution in patients with autoimmune disorders

b. Reverse transcriptase inhibitors
   i. In general, lamivudine and telbivudine are not preferred as first-line therapies because of high rates of resistance.
   ii. All reverse transcriptase inhibitors carry a black box warning for the development of lactic acidosis and severe hepatomegaly with steatosis. Monitor for worsening liver function tests, and periodically assess renal function. Female and obese patients are at higher risk. Reductions in bone mineral density (BMD) have been associated with long-term use. Assess baseline BMD in patients older than 12 years with a history of pathologic fracture or osteoporosis.
   iii. Tenofovir and entecavir are preferred antivirals in HBV with decompensated cirrhosis, where they are safer than pegylated interferon and have higher potency and minimal risk of resistance compared with other antivirals.
   iv. Entecavir (Baraclude)
      (a) Indicated for HBeAg-negative and HBeAg-positive patients with persistently elevated AST or ALT or histologically active disease; effective in lamivudine-resistant YMDD mutants
      (b) Reduces HBV DNA by up to 6.86 log in HBeAg-positive, naive patients and by 5.2 log in HBeAg-negative patients or those with lamivudine resistance
      (c) Dose: 0.5 mg orally once daily for patients older than 16 years and nucleoside naive; 1 mg orally once daily for patients older than 16 years with HBV viremia while receiving lamivudine or in lamivudine-resistant HBV
      (d) Dose adjustments required for renal impairment
      (e) Toxicity: Similar to lamivudine with headache, cough, upper respiratory infection, abdominal pain; possibly fewer ALT flares. Rare lactic acidosis. Resistance reported as similar to 1% at 5 years.
   v. Tenofovir (Viread 300 mg, Vemlidy 25 mg)
      (a) Nucleotide analog, formulated as tenofovir disoproxil fumarate (Viread) or tenofovir alafenamide (Vemlidy), indicated for chronic HBV infection
      (b) Effective for lamivudine-resistant HBV
      (c) Dose adjustments required for renal impairment
      (d) Toxicity: Overall, well tolerated; headache, nausea, and nasopharyngitis most commonly reported; potential renal toxicity, so periodic monitoring of SCr recommended; potential ALT flares on withdrawal; rare lactic acidosis. Tenofovir alafenamide is associated with less renal and bone toxicity.
   vi. HBV Treatment is summarized in Table 19

Table 19. Summary of Treatment Recommendations for Chronic HBV Infection in Adults

HBV Population	Preferred Treatment Options	Duration	Comments
HBeAg positive	Entecavir and tenofovir are preferred oral agents; use of the other oral reverse transcriptase inhibitors is possible but not preferred	Minimum of 1 yr	Preferred if contraindications or no response to IFNα
	PEG-IFNα	48 wk	If contraindication or no response, use entecavir and tenofovir
HBeAg negative	Entecavir and tenofovir are preferred oral agents; use of the other oral reverse transcriptase inhibitors is possible but not preferred	> 1 yr	Preferred if contraindications or no response to IFNα
	PEG-IFNα	≥ 1 yr	If contraindication or no response, use entecavir and tenofovir
Development of resistant HBV	Lamivudine, telbivudine, or entecavir resistance: Add or switch to tenofovir Adefovir resistance: Add or switch to entecavir Multidrug resistance: Combined tenofovir and entecavir	N/A	Confirm resistance with genotypic testing; reinforce adherence to therapy

N/A = not applicable; PEG-IFNα = pegylated interferon alfa.

4. Preventive strategies
    a. Vaccination (preexposure); indicated in the following groups:
        i. All infants
        ii. Unvaccinated children younger than 19 years
        iii. Individuals at risk of infection by sexual exposure (sex partners of HBsAg-positive individuals; sexually active individuals not in a long-term, mutually monogamous relationship; individuals seeking evaluation or treatment for a sexually transmitted infection; men who have sex with men)
        iv. Individuals at risk of infection by percutaneous or mucosal exposure to blood (those who have ever injected drugs; household contacts of HBsAg-positive individuals; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with a reasonably anticipated risk of exposure to blood or blood-contaminated body fluids; hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients; individuals with diabetes 19–59 years of age; individuals with diabetes 60 years and older at the discretion of the treating clinician)
        v. Others (international travelers to countries with high or intermediate levels of endemic HBV infection (HBsAg prevalence of 2% or greater); individuals with hepatitis C virus infection; individuals with chronic liver disease; individuals with HIV infection; incarcerated individuals; all other individuals seeking protection from HBV infection)

b. Available HBV vaccines (dose schedules vary by age)
   i. Dose schedules (Table 20)

Table 20. Dose Schedules for Hepatitis B Vaccinations

Vaccine[a]	Intramuscular Dose[b]	Schedule
Heplisav-B	≥ 18 yr: 0.5 mL	Two doses (0 and 1 mo)
Engerix-B	Birth – 19 yr: 0.5 mL ≥ 20 yr: 1 mL	Three doses (0, 1, and 6 mo)
	Adults receiving hemodialysis: 2 mL	Four doses (0, 1, 2, and 6 mo)
Recombivax HB	Birth – 19 yr: 0.5 mL[c] ≥ 20 yr: 1 mL	Three doses (0, 1, and 6 mo)
	Adults receiving hemodialysis: 1 mL of high-dose formulation (40 mcg)	Three doses (0, 1, and 6 mo)
Twinrix (HAV and HBV)	≥ 18 yr: 1 mL	Three doses (0, 1, and 6 mo)

[a]All listed vaccines should be refrigerated (2°C–8°C). Do not freeze.

[b]All listed vaccines should be administered intramuscularly in the deltoid muscle for adults, adolescents, and children ≥ 1 yr whose deltoid is large enough for intramuscular injection. For children < 1 yr, the anterolateral aspect of the thigh should be used as the intramuscular injection site.

[c]Ages 11–15 alternative dosing schedule: two intramuscular doses of 10 mcg/1 mL at 0 and 4–6 mo.

HAV = hepatitis A virus.

   ii. Obtain titers 1–2 months after the third dose of the series for HCPs.
   iii. HBV vaccines are available as combination products with HAV (Twinrix), DTP/IPV (Pediarix), and Hib (Comvax).

c. Postexposure prophylaxis
   i. Exposure can result in the need for HBV vaccine or immune globulin.
   ii. Doses of HBV immune globulin are 0.06 mL/kg intramuscularly and must be given within 7 days of exposure.
   iii. Patient populations requiring postexposure prophylaxis
      (a) Perinatal transmission
         (1) Children born to HBsAg-positive mothers should receive the first dose of the three-dose vaccine series plus HBV immune globulin within 12 hours of birth.
         (2) Children born to mothers with unknown HBsAg status (but suspected) should receive the first dose of the three-dose vaccine series within 12 hours of birth; testing should be performed on the child, and if positive, HBV immune globulin should be administered within 1 week.
         (3) Infants weighing less than 2 kg at birth whose mothers are documented as HBsAg negative should receive the first dose of the vaccine series 1 month after birth or at hospital discharge, whichever comes first.
      (b) Sexual contact or household contact with an infected person: Should receive HBV immune globulin plus vaccine series if exposed person is previously unvaccinated
      (c) Sexual contact or household contact with an HBV carrier: Should receive vaccine series if exposed person was previously unvaccinated

(d) Postexposure recommendations for HCPs (Table 21)

Table 21. Centers for Disease Control and Prevention Recommendations for Management of HBV Postexposure for HCPs

HBV Status of HCP	Postexposure Testing		Postexposure Prophylaxis		Postvaccination Serologic Testing
	Source Patient (HBsAg)	HCP Testing (anti-HBs)	HBIG	Vaccination	
Documented responder	No action needed				
Documented nonresponder after six doses	Positive or unknown	—	HBIG × 2 separated by 1 mo	—	No
	Negative	No action needed			
Response unknown after one complete series	Positive or unknown	<10 mIU/mL	HBIG × 1	Initiate revaccination	Yes
	Negative	<10 mIU	None		
	Any result	≥10 mIU	No action needed		
Unvaccinated or incompletely vaccinated or vaccine refusers	Positive or unknown	—	HBIG × 1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

HBIG = hepatitis B immune globulin; HCP = health care provider.

D. HCV
   1. Background
      a. RNA virus: six genotypes (50 subtypes)
         i. Genotype 1 (subtypes 1a, 1b, and 1c) accounts for 70%–75% of infections in the United States.
         ii. Genotypes 2 (subtypes 2a, 2b, and 2c) and 3 (3a and 3b) are less common in the United States.
         iii. Genotype helps determine therapy duration and likelihood of responding to therapy.
      b. Leading cause of liver disease and liver transplantation in the United States; also a common cause of hepatocellular carcinoma
      c. Viral replication occurs in the hepatocyte (virus is not directly cytopathic).
      d. Transmission is mainly bloodborne (transfusion, intravenous drug abuse).
         i. High risk
            (a) Transfusion
            (b) Intravenous drug abuse
            (c) Men who have unprotected sex with men
            (d) Hemodialysis
            (e) Incarceration
         ii. Low risk
            (a) Snorting cocaine or other drugs
            (b) Occupational exposure
            (c) Body piercing and acupuncture with unsterilized needle
            (d) Tattooing in unregulated settings
            (e) From pregnant mother to child
            (f) Nonsexual household contacts (rare)
            (g) Sharing razors or toothbrushes
            (h) Sexual transmission

e. Associated with acute and chronic infection; after acute infection, most patients (60%–85%) develop chronic infection

2. Clinical features: About 30% of patients are asymptomatic.
   a. Acute infection: Symptoms present 4–12 weeks after exposure; most patients are asymptomatic and seldom progress to fulminant disease; those who develop symptoms have nonspecific findings such as malaise, weakness, anorexia, and jaundice.
   b. *Chronic infection* is defined as the presence of viral RNA in the serum for 6 months or more.
      i. It may be associated with the long-term development of end-stage liver disease, cirrhosis, hepatocellular carcinoma.
      ii. Progression to complications and end-stage liver disease can be accelerated by concurrent alcohol use and coinfection with HIV; younger female patients have slower progression.
   c. Extrahepatic manifestations: rheumatoid symptoms, glomerulonephritis, cryoglobulinemia
3. Diagnosis and monitoring
   a. Clinical signs and symptoms include nausea, abdominal pain, jaundice, fever, malaise, or anorexia. Many patients have asymptomatic disease.
   b. Populations to test
      i. Suspected exposure
      ii. HIV infection
      iii. Intravenous or intranasal drug abuse
      iv. Receipt of clotting factors before 1987 or blood before 1992
      v. Hemodialysis
      vi. Abnormal ALT
      vii. Those receiving an organ transplant before 1992, including those who were ever incarcerated
      viii. Adults born between 1945 and 1965 should receive a one-time test for HCV.
      ix. Getting a tattoo in an unregulated setting
      x. Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood.
      xi. Unexplained chronic liver disease and chronic hepatitis, including elevated ALT
      xii. Annual testing for injection drug users and HIV-positive men who have unprotected sex with men or others with ongoing risk factors for HCV exposure
   c. Laboratory
      i. Serum anti-HCV antibodies (99% sensitivity and specificity [enzyme immunoassays]) are used as an initial screening for HCV. The presence of anti-HCV antibody does not confer protective immunity from subsequent infection.
         (a) If serum anti-HCV antibodies are positive, confirmatory testing by a sensitive HCV RNA test is warranted.
         (b) Quantitative HCV RNA testing to document baseline viremia before initiating antiviral therapy
         (c) Sustained virologic response (SVR) is undetectable HCV RNA 12 weeks after completion of treatment; it is considered a virologic cure.
      iii. Liver biopsy, imaging, or noninvasive markers to evaluate liver fibrosis is recommended.
      iv. Genotyping: Genotype 1 is the most common genotype in the United States; it is also the least responsive to treatment. Genotypes 2 and 3 are the other two most common genotypes in the United States.

4. Treatment
    a. Acute HCV infection
        i. Preexposure or postexposure prophylaxis is not recommended.
        ii. Monitor hepatic panel at 2- to 4-week intervals and HCV RNA every 4–6 weeks for 6–12 months to detect spontaneous clearance. If the decision is to treat, monitor for at least 12 weeks to 16 weeks to detect spontaneous clearance.
        iii. The same regimens used for chronic HCV are recommended for treatment.
    b. Chronic infection
        i. Therapy goal is to attain a SVR, defined as the absence of detectable HCV RNA 12 weeks after treatment. Obtaining undetectable concentrations at 12 weeks is considered a clinical cure.
        ii. With the availability of direct-acting antivirals (DAAs) therapies, treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be altered by treating HCV, transplantation, or other directed therapy.
        iii. DAAs carry a risk of reactivation of HBV infection. Patients receiving DAA therapy should be tested and monitored for HBV reactivation.
    c. Ribavirin in the treatment of HCV infection
        i. Oral nucleoside analog
        ii. Available as 200-mg tablets (Copegus) or capsules (Rebetol, Ribasphere; generic available)
        iii. Weight-based dosing of ribavirin, administered daily in two divided doses: for patients weighing less than 66 kg: 800 mg daily; 66–80 kg: 1000 mg daily; 81–105 kg: 1200 mg daily; greater than 105 kg: 1400 mg/day. Reduced dosing may be considered in patients with decompensated cirrhosis.
        iv. Significant adverse effect profile
            (a) Hemolytic anemia can occur in up to 10% of patients (usually within 1–2 weeks of initiating therapy); may worsen underlying cardiac disease; monitor complete blood cell count (CBC) at baseline, 2 weeks, 4 weeks, and periodically thereafter. In patients with no cardiac history, decrease the dose to 600 mg/day if hemoglobin drops to 10 g/dL or less, and discontinue when hemoglobin drops to 8.5 g/dL or less. In patients with a cardiac history, decrease the dose to 600 mg/day if hemoglobin drops more than 2 g/dL in any 4-week period during treatment. Discontinue if hemoglobin drops to less than 12 g/dL 4 weeks after dose reduction. Epoetin or darbepoetin can be used to stimulate red blood cell production, improve anemia, and sustain initial starting dose. It is also necessary to confirm that iron study results are normal and within range during treatment.
            (b) Teratogenicity: category X drug; requires a negative pregnancy test at baseline and every month up to 6 months after treatment, as well as the use of two forms of barrier contraception during treatment and for 6 months after treatment; applies to women taking the drug and female partners of male patients taking ribavirin
            (c) Other possible adverse events include pancreatitis, pulmonary dysfunction (dyspnea, pulmonary infiltrate, and pneumonitis), insomnia, irritability or depression (often called "riba rage"), and pruritus.
    d. NS5B/A polymerase inhibitors sofosbuvir (Sovaldi) and sofosbuvir/ledipasvir (Harvoni)
        i. Indications
            (a) Sofosbuvir: HCV genotypes 1, 2, 3, and 4, including those with hepatocellular carcinoma meeting Milan criteria and those with HCV/HIV coinfections
            (b) Sofosbuvir/ledipasvir: genotype 1, 4, 5, or 6 infection
        ii. Dosing: 400-mg tablet once daily with or without food
            (a) Sofosbuvir renal dosing: no dosing recommendations for glomerular filtration rate (GFR) less than 30 mL/minute. Sofosbuvir and metabolite accumulate in severe renal impairment.

iii. Adverse effects: fatigue, headache
iv. Drug interactions
(a) Avoid use with potent P-glycoprotein (P-gp) inducers.
(b) Concentrations are significantly affected by anticonvulsants (carbamazepine, phenytoin, phenobarbital, and oxcarbazepine), rifabutin, rifampin, St. John's wort, and tipranavir/ritonavir.
(c) Avoid using with amiodarone because of symptomatic bradycardia. The mechanism of this interaction is not known.

e. NS5A inhibitor daclatasvir (Daklinza)
i. Indication: Genotype 1 or 3 infection in combination with sofosbuvir. SVR rates are reduced in the presence of cirrhosis.
ii. Dosing: 60 mg once daily with or without food; no dosage adjustments required for renal or hepatic dysfunction
iii. Adverse effects: Headache, fatigue, nausea, diarrhea
iv. Drug interactions
(a) When administered with strong CYP3A4 inhibitors, reduce dose to 30 mg daily (e.g., ritonavir, clarithromycin, itraconazole, ketoconazole).
(b) When administered with moderate CYP3A4 inducers, increase dose to 90 mg daily (e.g., bosentan, dexamethasone, efavirenz, etravirine).
(c) Contraindicated in combination with strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort)

f. NS3/4A inhibitor Grazoprevir combined with NS5A inhibitor elbasvir (Zepatier)
i. Indication: Geonotypes 1 or 4 infection with or without ribavirin
ii. Dosing: Grazoprevir 100 mg / elbasvir 50 mg fixed-dose combination tablet once daily for 12 or 16 weeks.
(a) Testing for NS5A resistance-associated substitutions (RASs) is recommended. If RASs are present, treatment duration should be extended to 16 weeks, and ribavirin should be coadministered.
(b) Renal dose adjustment is not necessary, including patients receiving hemodialysis.
iii. Adverse effects
(a) ALT elevations: Check ALT at baseline, 8 weeks of therapy, and 12 weeks of therapy if 16 week duration is indicated (contraindicated in Child-Pugh class B or C).
(b) Headache, fatigue
iv. Drug interactions
(a) Contraindicated in combination with OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz. Vosevi, Mavyret, and Zepatier are associated with rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment and should be avoided in these patients.

g. NS5A/B inhibitor combination velpatasvir / sofosbuvir (Epclusa)
i. Indication: Genotype 1–6 infection
ii. Dosing: velpatasvir 100 mg / sofosbuvir 400 mg fixed-dose combination tablet once daily for 12 weeks. Weight-based ribavirin is added if decompensated cirrhosis is present with HCV genotypes 1–4.
iii. Adverse effects: headache and fatigue
iv. Drug interactions
(a) Contraindicated with inducers of P-gp and moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine), which can decrease plasma concentrations of sofosbuvir and/or velpatasvir.
(b) Avoid use of amiodarone and sofosbuvir because of symptomatic bradycardia.

h. NS5A/B and NS3/4A inhibitor combination velpatasvir, sofosbuvir, and voxilaprevir (Vosevi)
   i. Indications
      (a) Genotypes 1–6 infection with or without compensated cirrhosis (Child-Turcotte-Pugh A) in patients who have been treated with an HCV regimen containing an NS5A inhibitor.
      (b) Genotypes 1a or 3 who have been treated with a sofosbuvir-containing regimen without an NS5A inhibitor
   ii. Dosing: sofosbuvir 400 mg / velpatasvir 100 mg / voxilaprevir 100 mg fixed dose combination tablet once daily with food for 12 weeks
   iii. Adverse effects: headache, fatigue, diarrhea, nausea. Vosevi, Mavyret, and Zepatier are associated with rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment and should be avoided in these patients.
   iv. Drug interactions: See velpatasvir / sofosbuvir (Epclusa) listing above.

i. NS3/4A and NS5A inhibitor combination glecaprevir and pibrentasvir (Mavyret)
   i. Indications
      (a) Genotype 1–6 infection with or without compensated cirrhosis (Child-Turcotte-Pugh A)
      (b) Genotype 1 infection in patients who have previously been treated with either an NS5A inhibitor or an NS3/4A inhibitor, but not both
   ii. Dosing: glecaprevir 100 mg / pibrentasvir 40mg fixed dose combination tablet, three tablets once daily with food for:
      (a) Eight weeks for genotype 1–6 treatment-naive patients without cirrhosis
      (b) Twelve weeks for genotype 1–6 treatment-naive patients with compensated cirrhosis
      (c) Eight to 16 weeks for patients previously treated, depending on prior regimen
   iii. Adverse effects: headache, fatigue, nausea. Vosevi, Mavyret, and Zepatier are associated with rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment and should be avoided in these patients.
   iv. Drug interactions: Avoid use with P-gp or CYP3A inducers, because this can reduce the concentration of glecaprevir and pibrentasvir (carbamazepine, efavirnez, St. John's wort). It is contraindicated with atazanavir or rifampin.

j. Treatment recommendations for chronic HCV infection in treatment-naive adults are included in Table 22.

Table 22. Simplified Treatment Algorithm for Treatment-Naive Adult Patients with HCV (irrespective of genotype unless noted)

Patients without Cirrhosis	Patients with Compensated Cirrhosis (Child-Pugh-Turcotte class A)
Glecaprevir (300 mg)/pibrentasvir (120 mg) daily with food × 8 wk Sofosbuvir (400 mg)/velpatasvir (100 mg) daily × 12 wk	Glecaprevir (300 mg)/pibrentasvir (120 mg) daily with food × 8 wk Sofosbuvir (400 mg)/velpatasvir (100 mg) daily × 12 wk for genotypes 1, 2, 4, 5, or 6. Genotype 3 requires baseline NS5A RAS testing. Sofosbuvir/velpatasvir can be used if Y93H is absent

HCV = hepatitis C virus; RAS = resistance-associated substitution.

5. Monitoring
   a. Baseline HCV RNA, genotype, quantitative HCV RNA (HCV viral load), CBC, liver function tests (LFTs), and calculated GFR. Pregnancy test for women receiving ribavirin. Evaluate for potential drug-drug interactions.

b. On therapy: Medication adherence, potential drug-drug interactions, HCV viral load, CBC, SCr, calculated GFR, LFTs at 4 weeks, then as clinically indicated.
c. After treatment: Check HCV RNA at 12 weeks to assess for SVR.

6. Prevention of HCV
   a. No vaccine or immune globulin available
   b. Risk factor modification
      i. Intravenous drug abuse: Methadone maintenance, syringe exchange
      ii. Sexual contact: Appropriate barrier contraception
      iii. Avoid blood exposure: Occupational (universal precautions) or other contact (e.g., sharing toothbrushes or razors or receiving a tattoo)
      iv. The HAV and HBV vaccine to prevent further progression of liver disease

Patient Cases

8. A 45-year-old woman with a history of intravenous drug abuse is evaluated in the clinic for chronic HBV infection. Although she received the HBV diagnosis 8 months ago, she has not been treated for it. Laboratory values today include HBsAg positive, HBeAg positive, AST 650 IU/mL, ALT 850 IU/mL, HBV DNA 107,000 IU/mL, SCr 1.9 mg/dL, INR 1.3, and albumin 3.9 g/dL. She has no evidence of ascites or encephalopathy. A liver biopsy reveals severe necroinflammation and bridging fibrosis. Resistance testing reveals the YMDD mutation. Which is the best course of action?

   A. Withhold drug therapy and recheck HBV DNA in 6 months.
   B. Initiate entecavir 0.25 mg/day.
   C. Initiate lamivudine 100 mg/day.
   D. Initiate tenofovir disoproxil fumarate 300 mg/day.

9. A 38-year-old white man (height 72 inches, weight 75 kg) is seen today for a new diagnosis of chronic HCV, genotype 1a. Pretreatment laboratory values include AST 350 IU/mL, ALT 420 IU/mL, HCV RNA 950,000 IU/mL, SCr 1 mg/dL, hemoglobin 12 g/dL, and WBC 12 × 10^3 cells/mm^3. A liver biopsy reveals a Metavir score of F3/A2, and overall, he has compensated liver disease. He reports no known drug allergies. Which option is best for treating this patient's chronic HCV infection?

   A. Withhold therapy and reassess in 12 months.
   B. Initiate glecaprevir and pibrentasvir.
   C. Initiate sofosbuvir and ledipasvir.
   D. Initiate pegylated interferon, ribavirin, and sofosbuvir.

VII. NAUSEA AND VOMITING

A. Definitions and Pathophysiology
   1. Definitions
      a. Nausea: Unpleasant sensation of the imminent need to vomit; may or may not lead to vomiting
      b. Vomiting: Forceful expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature
   2. Pathophysiology
      a. Stimuli for vomiting are processed through several major anatomic areas, each of which has various receptors associated with input to the medullary vomiting center.

i. Visceral stimuli: Mediated through dopamine and serotonin receptors. Major stimuli include:
   (a) Gastric irritants
   (b) Nongastric stimuli (peritonitis, intestinal or biliary distension, pancreatitis, gastroparesis)
   (c) Abdominal radiation
   (d) Chemotherapeutic agents
   (e) Pharyngeal stimulation

ii. Chemoreceptor trigger zone (located in the area postrema): Mediated by dopamine (D_2), serotonin, and some histamine (H_1) and muscarinic (M_1) and substance P/neurokinin 1; major stimuli include:
   (a) Medications: Opiates, dopamine agonists, digoxin, chemotherapeutic agents, macrolides, general anesthetics
   (b) Metabolic disturbances (uremia, diabetic ketoacidosis, hypercalcemia, hypoxemia)
   (c) Bacterial toxins
   (d) Radiation therapy

iii. Vestibular labyrinths: Mediated through H_1 and M_1. Major stimuli include:
   (a) Motion sickness
   (b) Labyrinth infection

iv. Cerebral cortex: Receptor involvement not well characterized; noxious odors, visions, and tastes

Table 23. Common Clinical Conditions Associated with Nausea and Vomiting

Category	Conditions
Infectious	Viral or bacterial gastritis or gastroenteritis, pyelonephritis
Gastrointestinal	Pancreatitis, gastroparesis, hepatitis, gastroesophageal reflux disease
Central nervous system	Migraine, stroke, pain, seizures, motion sickness, meningitis
Endocrine or metabolic	Pregnancy, uremia, diabetic ketoacidosis, hypercalcemia
Cardiovascular	Myocardial infarction, heart failure
Other	Postoperative, cerebral mass

b. Clinical consequences of nausea and vomiting include dehydration, electrolyte disturbances, aspiration, and Mallory-Weiss syndrome.

B. Treatment and prevention strategies
   1. Remove or treat the underlying cause (Table 23)
   2. Correct dehydration and electrolyte disturbances. Oral rehydration is preferred, if possible, with oral rehydration solutions (e.g., Pedialyte, diluted Gatorade).
   3. Drug treatment: Use drugs that target receptors involved with stimuli. May need combination of drugs with different mechanisms. Also may need alternative dose forms (intravenous, subcutaneous, suppository).
      a. Major drug classes of antiemetics: All are antagonists at the respective receptors. (Table 24)
      b. Drugs of choice for different situations include:
         i. General medical use: phenothiazines, serotonin antagonists
         ii. Chemotherapy induced: serotonin antagonists, NK1 antagonists, corticosteroids (See "Oncology Supportive Care" chapter for treatment and prevention.)
         iii. Postoperative: serotonin antagonists, scopolamine, corticosteroids
         iv. Motion sickness: antihistamines, scopolamine
         v. Pregnancy: phosphorylated carbohydrate solution, pyridoxine, antihistamines, ginger
         vi. Gastroparesis: metoclopramide

Table 24. Select Antiemetics

Drug	Formulations	Comments
Phenothiazines		
Promethazine (Phenergan)	Tablet, suppository, injection	Antidopaminergic, anticholinergic, and antihistaminergic activity; can cause EPS, injection-site irritation (do not use subcutaneously), sedation, anticholinergic effects; IV formulation should be diluted (risk of tissue necrosis)
Prochlorperazine (Compazine)	Tablet, syrup, suppository, injection	Mainly antidopaminergic activity; can cause EPS, injection-site irritation (do not use subcutaneously)
Serotonin antagonists		
Ondansetron (Zofran)	Tablet, ODT, oral solution, injection, oral-soluble film (Zuplenz)	Overall, well tolerated; no liquid required for ODT or soluble film; contraindicated with apomorphine; associated with QTc prolongation; correct hypomagnesemia and hypokalemia
Granisetron (Kytril, Sancuso, Sustol)	Injection, tablet, oral solution, patch	Overall, well tolerated; associated with QTc prolongation
Dolasetron (Anzemet)	Injection, tablet	Typically, a one-time dose; contraindicated with apomorphine; associated with QTc prolongation; correct hypomagnesemia and hypokalemia
Palonosetron (Aloxi)	Injection	Long duration of action is 24 hr to 5 days; only one dose required
Antihistamines		
Dimenhydrinate (Dramamine), cyclizine (Marezine), meclizine (Bonine), doxylamine (Unisom)	Tablet, oral liquid, injection	Take 30–60 min before travel; risk of sedation and anticholinergic adverse effects
Butyrophenones		
Haloperidol, droperidol	Injection, tablet	Risk of extrapyramidal adverse effects; risk of QTc prolongation; requirement for baseline ECG and 2- to 3-hr postdose cardiac monitoring
Neurokinin 1 antagonists		
Aprepitant, fosaprepitant (Emend)	Capsule, injection	Targets substance P/neurokinin 1 (NK1) receptors; reduces efficacy of warfarin and oral contraceptives; dose-dependent inhibitor of CYP3A4
Netupitant / palonosetron (Akynzeo)	Capsule	Targets substance P/neurokinin 1 (NK1) receptors and 5-HT3; avoid in severe renal or hepatic disease, drug-drug interactions by CYP enzymes
Rolapitant (Varubi)	Tablet	Targets neurokinin 1 (NK1) receptors; long half-life (7 days)
Miscellaneous agents		
Scopolamine (Transderm Scop)	Patch	Apply behind ear 4 hr before travel; can wear for up to 72 hr; do not cut patch; risk of anticholinergic adverse effects
Dronabinol (Marinol), nabilone (Cesamet)	Capsule	Delta-9 tetrahydrocannabinol; targets central endogenous cannabinoid receptors; used most often for chemotherapy-induced N/V; can cause appetite stimulation, euphoria, cognitive impairment
Phosphorylated carbohydrate solution (Emetrol)	Oral solution	Use undiluted for best effect; do not use >1 hr (or maximum of five doses); safe in pregnancy; avoid in diabetes and fructose intolerance
Doxylamine/ pyridoxine (Diclegis, Bonjesta)	Delayed-release tablet (10 mg/10 mg)	Prescription product approved for NVP in women who do not respond to conservative management; OTC doxylamine and pyridoxine may be considered; pregnancy category A

CYP = cytochrome P450; ECG = electrocardiogram; EPS = extrapyramidal symptoms; N/V = nausea and vomiting; NVP = nausea and vomiting of pregnancy; ODT = orally disintegrating tablet; SR = sustained release.

c. Nondrug therapy for nausea and vomiting: acupressure and acustimulation wristbands (Sea-Band, Reliefband); work by stimulating the pericardium 6 (P6) point.

VIII. PANCREATITIS

A. Classification and pathophysiology
   1. Acute
      a. Characterized by inflammation in the pancreas ranging from mild to severe
      b. An initial insult leads to the release of trypsin in the pancreas, leading to the activation of pancreatic enzymes and intrapancreatic inflammation and complications. It can then progress to extrapancreatic complications. It is usually reversible once the underlying cause is addressed.
      c. Two distinct phases
         i. Early (within 1 week): associated with systemic inflammatory response syndrome or organ damage
         ii. Late (more than 1 week): associated with local complications
      d. Typical signs and symptoms include abdominal pain and distension, nausea, vomiting, jaundice, and fever.
         i. Local complication: necrosis, hemorrhage, pseudocyst, abscess, infection
         ii. Systemic complications: systemic inflammatory response syndrome, acute respiratory distress syndrome, shock, organ failure
      e. Main causes of acute pancreatitis
         i. Long-term alcohol abuse
         ii. Gallstones
         iii. Drugs (Box 5)

Box 5. Common Causes of Drug-Induced Pancreatitis

Amiodarone
Asparaginase
Azathioprine/mercaptopurine
Cannabis
Didanosine
Diuretics (furosemide, hydrochlorothiazide)
Estrogens
Exenatide
Mesalamine/sulfasalazine
Pentamidine
Sitagliptin
Tetracycline
Trimethoprim/sulfamethoxazole
Valproic acid

         iv. Post–endoscopic retrograde cholangiopancreatography
         v. Hypertriglyceridemia (generally greater than 1000 mg/dL)
         vi. Idiopathic
         vii. Structural abnormalities
         viii. Toxins (scorpion venom)
         ix. Trauma
         x. Ischemia

2. Chronic
    a. Characterized by irreversible structural and functional loss of pancreatic function caused by long-standing inflammation and repeated injury
    b. Repeated injury results in loss of both exocrine and endocrine function.
    c. Typical signs and symptoms include chronic abdominal pain, steatorrhea, weight loss or cachexia, jaundice, and hyperglycemia. Complications include diabetes, pseudocysts, calcification, ascites, and biliary stricture.
    d. Risk factors for chronic pancreatitis are based on the M-ANNHEIM classification. The M-ANNHEIM classification system is an objective, relatively noninvasive approach to categorizing patients with acute or chronic pancreatitis on the basis of their disease etiology, clinical stage, and disease severity.
    M = Multiple risk factors
    A = Alcohol consumption
    N = Nicotine
    N = Nutritional factors (high fat and protein, hyperlipidemia)
    H = Hereditary factors
    E = Efferent duct factors
    I = Immunologic factors
    M = Miscellaneous and rare factors (includes drugs)

B. Diagnosis
    1. Acute pancreatitis
        a. Diagnosis is typically based on two of the three following criteria:
            i. Presence of abdominal pain
            ii. Laboratory diagnosis: Serum lipase (greater than 3 times the ULN) is the most sensitive test. Patients may also have hyperglycemia and other electrolyte abnormalities related to vomiting. Patients often have a leukocytosis and a fever.
            iii. Imaging: Abdominal ultrasonography and computed tomography (CT) scan to evaluate pancreas, biliary system, and presence of local complications
        b. Severity and prognosis (Table 25)

Table 25. Common Scoring Systems to Classify Severity and Prognosis of Acute Pancreatitis

Atlanta Symposium Criteria for Acute Pancreatitis	Ranson Criteria for Prognosis[a]	
Mild: absence of organ failure or local complications Moderately severe: local complications or transient organ failure (< 48 hr) Severe: persistent organ failure > 48 hr	At admission: Age > 55 yr (>70 yr) WBC >16,000/L (18,000/L) Blood glucose > 200 mg/dL (220 mg/dL) Serum lactate dehydrogenase > 350 IU/L (>400 IU/L) Serum AST > 250 IU/L (same)	Within next 48 hr: Decrease in hematocrit by > 10% (same) Estimated fluid sequestration of > 6 L (4 L) Serum calcium < 8 mg/dL (same) Pao_2 < 60 mm Hg (omitted) BUN concentration increase > 5 mg/dL after IV fluid hydration (> 2 mg/dL) Base deficit of > 4 mmol/L (6 mmol/L)

[a]Values in parentheses are for gallstone induced; meeting more than three criteria indicates severe disease.

AST = aspartate transaminase; BUN = blood urea nitrogen; WBC = white blood cell count.

2. Chronic pancreatitis: Diagnosis is typically based on the clinical signs and symptoms plus laboratory and imaging.
    a. Laboratory diagnosis: Serum lipase may be normal; hyperglycemia and low albumin or prealbumin may also be present.
    b. Imaging: CT scan may reveal pancreatic calcification or pseudocyst.

C. Treatment strategies
1. Acute pancreatitis: Treatment is largely supportive; should include removal or treatment of underlying cause if possible.
    a. Temporarily withhold oral intake and provide rehydration with intravenous fluids, typically 250–500 mL/hour of lactated Ringer or normal saline solution. Treat electrolyte disturbances (hypokalemia, hypocalcemia, hyperglycemia).
    b. Pain management involves the use of intravenous narcotics (avoid meperidine). Patient-controlled analgesia is often used.
    c. Antiemetics: Intravenous ondansetron, prochlorperazine, or promethazine
    d. Nutrition: If pancreatitis is mild, then early (less than 24 hours) oral feeding can be resumed if no vomiting is present. If severe pancreatitis is present, use enteral nutrition to prevent infectious complications. Avoid total parenteral nutrition (higher rates of infection, mortality, and length of stay).
    e. Antibiotics, in general, are not recommended for routine prophylaxis in severe pancreatitis. Antibiotics can be used if extrapancreatic infection is present. If infected necrosis is present, then carbapenems, fluoroquinolones, or metronidazole may be useful in delaying the need for intervention.
    f. Endoscopic retrograde cholangiopancreatography may be needed for cholangitis or gallstone pancreatitis. This is often followed by cholecystectomy to prevent future episodes.
2. Chronic pancreatitis: Treatment is largely symptomatic.
    a. Abstinence from alcohol is essential. Pharmacologic intervention and supportive care (e.g., Alcoholics Anonymous) may be needed. Smoking cessation is also recommended by the ACG guidelines (strong recommendation, very low-quality evidence).
    b. Antioxidant therapy can be considered to treat pain with chronic pancreatitis. The antioxidants used in clinical trials vary in type and dosage but commonly include selenium, ascorbic acid, beta-carotene, and methionine (conditional recommendation, moderate-quality of evidence).
    c. Pain management often requires a combination of nonnarcotic and narcotic analgesics (long-acting morphine, oxycodone, or transdermal fentanyl) in combination with pancreatic enzyme replacement. Avoid acetaminophen if long-term alcohol use is a factor.
    d. Antiemetics: Oral ondansetron, prochlorperazine, or promethazine as needed
    e. Nutrition: Goal is to maximize caloric intake and weight gain and reduce steatorrhea. May need more frequent, lower-fat meals and fat-soluble vitamin supplementation. Long-term enteral or parenteral nutrition may be required.
3. Pancreatic enzyme replacement therapy
    a. Simulate the digestion of food that normally occurs with normal pancreatic enzyme release to reduce maldigestion and malabsorption. Pancreatic enzyme replacement therapy is recommended if the patient experiences weight loss, malnutrition, diarrhea, steatorrhea, osteoporosis, or osteopenia (conditional recommendation, low level of evidence).
    b. Products are enteric-coated microspheres or microtablets that contain lipase, amylase, and protease. Meant to mix with food, they release enzymes at intestinal pH values greater than 5.5. Products should not be crushed or chewed.
    c. Enzyme products were historically considered nutritional supplements. The FDA has now mandated FDA approval of all enzyme products. (Table 26)

Table 26. Selected Pancreatic Enzyme Replacement Products

Brand Name	Lipase (units)	Amylase (units)	Protease (units)	Formulation
Viokace	10,440	39,150	39,150	Immediate-release tablet
	20,880	78,300	78,300	
Creon	3,000	15,000	9,500	Capsules with enteric-coated microspheres (0.17–1.6 mm)
	6,000	30,000	19,000	
	12,000	60,000	38,000	
	24,000	120,000	76,000	
	36,000	180,000	114,000	
Zenpep	3,000	14,000	10,000	Capsules with enteric-coated beads (1.8–1.9 mm for 3000/5000 units; 2.2–2.5 mm for all other strengths)
	5,000	24,000	17,000	
	10,000	42,000	32,000	
	15,000	63,000	47,000	
	20,000	84,000	63,000	
	25,000	105,000	79,000	
	40,000	168,000	126,000	
Pancreaze	4,200	17,500	10,000	Capsules with enteric-coated microtablets (2 mm)
	10,500	43,750	25,000	
	16,800	70,000	40,000	
	21,000	61,000	37,000	
Pertzye	4,000	15,125	14,375	Capsules with bicarbonate-buffered enteric-coated microspheres (0.8–2 mm)
	8,000	30,250	28,750	
	16,000	60,500	57,500	
	24,000	90,750	86,250	

d. Dosing is based on the lipase content (units) of the product.
   i. Starting adult doses are generally 40,000–50,000 units per meal, with a half dose for snacks. May also use weight-based dosing of 500–1000 units/kg per meal for those older than 4 years.
   ii. Maximum dose is 2500 units/kg per dose, 10,000 units/kg/day, or 90,000 units per meal.
   iii. Give enzymes with meals as opposed to before or after meals.
   iv. Titrate according to weight gain and reduction in steatorrhea.
   v. May need to add PPI if maximal response is not seen.

e. Adverse effects of pancreatic enzyme therapy
   i. Nausea or abdominal cramping
   ii. Enzymes are derived from porcine pancreas; this is contraindicated if a pork allergy is present.
   iii. Hyperuricosuria, hyperuricemia
   iv. Fibrosing colonopathy (generally seen with doses greater than 10,000 units/kg/day)
   v. Pregnancy category C

IX. DIARRHEA

A. Classification and pathophysiology
   1. Clinical definition: Alteration in a normal bowel movement characterized by an increase in the water content, volume, or frequency (more than three per day) of stool
      a. *Acute* is generally considered less than 72 hours to 14 days.
      b. *Chronic* is generally considered more than 14–30 days.
   2. Can be classified into several major categories related to underlying cause
      a. Secretory
         i. Secondary to enhanced secretion by intestinal mucosa; often, large, watery volume with loss of electrolytes
         ii. Common causes: Bacterial or viral or bacterial enteritis, gastric hypersecretion, carcinoid, stimulant laxatives, bile acid malabsorption, celiac disease, IBD (mucosal)
      b. Osmotic
         i. Secondary to a hyperosmolar gradient in the intestinal lumen
         ii. Common causes: Osmotic laxatives, carbohydrate malabsorption (lactase deficiency), fat malabsorption (pancreatic insufficiency), short bowel syndrome
      c. Exudative or inflammatory
         i. Secondary to inflammation or infiltration or invasion of the intestinal mucosa
         ii. Common causes: IBD, invasive infection (*C. difficile* toxin, enterotoxigenic *Escherichia coli,* cytomegalovirus, *Shigella* species), ischemic colitis, radiation enterocolitis, neoplasm
      d. Altered motility or motor function
         i. Secondary to autonomic nerve dysfunction
         ii. Common causes: diabetic neuropathy, postvagotomy, hyperthyroidism, IBS, Addison disease
   3. Drug-induced diarrhea can occur by a variety of mechanisms. See Box 6 for a list of medications that commonly cause diarrhea.

Box 6. Common Causes of Drug-Induced Diarrhea

Acarbose or miglitol
Antibiotics
Antineoplastics
Colchicine
Digoxin
Laxatives
Levothyroxine (over-replacement)
Metoclopramide
NSAIDs
Prostaglandins (misoprostol)
Orlistat
Sorbitol (sugar-free products)

B. Diagnosis
   1. Conduct a thorough patient history.
      a. Evaluate for disease- and drug-induced causes (laxative, recent antibiotic use), recent travel history, and temporal relation to food intake.
      b. Assess fluid and electrolyte status.
      c. Assess CBC and stool culture, and evaluate for ova and parasites if infectious cause is suspected. Assess for *C. difficile* toxin and culture if there has been recent antibiotic use or hospitalization.

d. Evaluate stool pH, electrolytes, osmolarity, or fat content, if indicated.
e. Imaging (abdominal CT scan) or endoscopy with biopsy may be indicated, particularly for inflammatory diarrhea or suggestion of neoplasm or celiac disease.

2. Referral to higher level of care or further evaluation may be necessary for some patients.
   a. Immunocompromised
   b. Infants and children
   c. Pregnant women
   d. Presence of fever
   e. Blood in the stool
   f. Weight loss (greater than 5%)
   g. Suspected invasive infection

C. Treatment strategies
1. Removal or treatment of underlying causes, if possible
2. Rehydration
   a. Intravenous fluids appropriate for hospitalized patients
   b. Oral rehydration appropriate for all patients if no vomiting is present
      i. Sodium and glucose are key ingredients of oral rehydration solutions, because they have active uptake into the intestinal mucosa even during active diarrhea. This results in water being pulled back into circulation. Other formulations (popsicles) are also available.
      ii. Gatorade may need to be diluted because it has a large amount of carbohydrates.
3. Dietary modifications
   a. Avoid dairy products because transient lactase deficiency can occur.
   b. "BRAT" diet for adults (mild foods such as bananas, rice, applesauce, toast) is sometimes recommended for short-term use, though definitive supporting data are limited.
   c. May need to interrupt feedings for pediatric patients
4. Drug therapy for diarrhea is listed in Table 27 (see "Infectious Diseases" chapter for management of infectious causes)

Table 27. Select Therapies for the Management of Diarrhea

Drugs	Mechanism	Role	Adverse Effects and Precautions
Bismuth subsalicylate	Antisecretory, binds toxins	Mild-moderate diarrhea; prevention of traveler's diarrhea	Stool discoloration; avoid in salicylate allergy, age <12 yr, pregnancy, nursing; caution with anticoagulants; can bind other drugs; can interfere with some radiographic procedures
Crofelemer (Mytesi)	Gastrointestinal chloride channel inhibitor	Antiretroviral therapy-associated diarrhea in patients with HIV	Upper respiratory infection, bronchitis, cough, bilirubin elevation
Lactase	Enzyme	Lactase deficiency or intolerance	Well tolerated
Loperamide	μ-Receptor agonist	Mild to moderate noninvasive diarrhea; adjunctive to other non-opiate therapies	Minimal CNS effects; avoid if suspected invasive infection; pregnancy category B

CNS = central nervous system; GLP-2 = glucagon-like peptide-2.

Table 27. Select Therapies for the Management of Diarrhea *(continued)*

Drugs	Mechanism	Role	Adverse Effects and Precautions
Octreotide	Antisecretory suppression of hormone release	Treatment of tumor-associated diarrhea (VIPoma [Verner-Morrison syndrome], carcinoid); HIV-associated diarrhea	Hyperglycemia, gallstone formation
Opiates, tincture of opium, diphenoxylate plus atropine	μ-Receptor agonist	Moderate to severe noninvasive diarrhea; suboptimal response to loperamide or bismuth; refractory diarrhea	CNS effects, respiratory depression; constipation, possible anticholinergic effects with atropine; avoid if suspected invasive infection
Probiotics (*Lactobacillus*, *Saccharomyces* spp.)	Competition with pathogenic organisms, production of antimicrobial substances, enhancement of immune response	Prevention of antibiotic-associated diarrhea; adjunctive therapy for treatment of *C. difficile*; small intestinal bacterial overgrowth	Well tolerated; caution if severely immunocompromised
Teduglutide (Gattex)	GLP-2 analog	Approved for adult patients with short bowel syndrome who are dependent on parenteral support	Colonic neoplasms (colonoscopy recommended every 5 yr); intestinal obstruction; biliary/pancreatic disease (bilirubin, amylase, lipase, alkaline phosphatase, every 6 mo)

CNS = central nervous system; GLP-2 = glucagon-like peptide-2.

X. CONSTIPATION

A. Definition and pathophysiology
   1. Bowel symptoms (e.g., difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation) may occur in isolation or secondary to another underlying disorder. The 2013 guidelines distinguish between normal-transit constipation and slow-transit constipation. Another definition is "a symptom based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both." (Am J Gastroenterol 2014;109:S2-26)
   2. May also be characterized by difficulty with or incomplete evacuation, straining, or presence of hard, dry stools. Abdominal pain and distension can occur, as well as low back pain and anorexia.
   3. Pathophysiology is related to many different factors. Common causes include:
      a. Altered motility (e.g., ileus)
      b. Neurogenic causes (autonomic neuropathies, Parkinson disease)
      c. Endocrine or metabolic disorders (e.g., hypothyroidism, diabetes, hypokalemia, hypercalcemia, uremia)
      d. Pregnancy
      e. Psychogenic causes
      f. Structural abnormalities or obstruction

g. Nutritional (e.g., reduced fiber and water intake)
h. Medications (Box 7)

4. Constipation that is not caused by an underlying organic cause is called *chronic idiopathic constipation* (CIC) or functional constipation.

Box 7. Common Causes of Drug-Induced Constipation

Aluminum-containing drugs (antacids, sucralfate)
Antihistamines
Benzodiazepines
Bile acid sequestrants
Calcium channel blockers
Calcium supplements and antacids
Diuretics
Iron supplements
Opioids
Phenothiazines
Scopolamine, benztropine
Tricyclic antidepressants

B. Diagnosis
1. Evaluate patient history thoroughly.
a. Establish patient baseline and evaluate for disease- and drug-induced causes.
b. Assess fluid and electrolyte status, thyroid function
c. Imaging (abdominal CT scan or radiograph) may be necessary to assess for ileus, obstruction, or dilatation.

2. Referral for further evaluation may be necessary for some patient populations.
a. Symptoms for more than 1–2 weeks despite treatment
b. Considerable pain or cramping
c. Pregnancy
d. Presence of fever
e. Blood in the stool
f. Reduction in stool caliber
g. Weight loss
h. Paraplegia, quadriplegia

3. Diagnosis of CIC (functional constipation) is based on the Rome IV criteria, which is presence of two or more of the following over the previous 3 months:
a. Straining during at least 25% of defecations
b. Lumpy or hard stools in at least 25% of defecations
c. Sensation of incomplete evacuation for at least 25% of defecations
d. Sensation of anorectal obstruction or blockage for at least 25% of defecations
e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
f. Fewer than three defecations per week

C. Treatment strategies
   1. Remove or treat underlying causes, if possible.
   2. Nonpharmacologic interventions
      a. Increase fluid intake to 6–8 glasses of water per day, although minimal evidence to support efficacy if dehydration is not present.
      b. Increase dietary fiber to 20–30 g/day.
      c. Incorporate or increase exercise to 3–5 days/week.
      d. Modifying behaviors: Toilet training and toileting position
   3. Drug therapy for prevention and treatment of constipation (Table 28)
      a. Choose drug therapy on the basis of desired onset of action, patient preference, presence of potential contraindications, and use in special populations.
      b. Provide patient education on alternative dose forms (enema, suppository).

Table 28. Drug Therapy Options for Treatment and Prevention of Constipation

Drugs	Role	Comments
Saline osmotic laxatives		
Magnesium citrate, magnesium hydroxide, sodium phosphate	Acute or intermittent constipation, preoperative or preprocedure bowel preparation	Fast onset (15 min to 3 hr); avoid in renal impairment, HF, cirrhosis; FDA warning regarding oral sodium phosphate and development of acute phosphate nephropathy (avoid use for bowel preparations)
Osmotic laxatives		
Glycerin	Management of acute or intermittent constipation; used in pediatric patients	Suppository; fast onset (within 1 hr)
Lactulose	Management of acute, intermittent, or chronic constipation, including CIC; useful in concomitant in chronic liver disease	Onset 1–2 days (may require multiple doses); associated with gas and bloating; syrup or powder for solution
Polyethylene glycol	Acute or chronic constipation; effective for CIC; preoperative/ colon preparation	Onset 1–3 days; safe in renal and hepatic disease and pregnancy; overall, well tolerated; may be used long term
Stimulant laxatives		
Bisacodyl	Short-term relief of acute or intermittent constipation or as part of preoperative or colonoscopy bowel preparation	Oral onset 6–12 hr, suppository within 1 hr; oral tablets are enteric coated
Senna	Short-term relief of acute or intermittent constipation; often used long term for prevention of opioid-induced constipation	Tablet and liquid; onset 6–12 hr; can cause abdominal cramping, electrolyte disturbances, melanosis coli

Table 28. Drug Therapy Options for Treatment and Prevention of Constipation *(continued)*

Drugs	Role	Comments
Bulk-forming laxatives		
Psyllium inulin Inulin Wheat dextrin Calcium polycarbophil Methylcellulose	Intermittent or chronic constipation	Onset 12–72 hr; less effective in drug-induced constipation and STC; requires adequate water intake to be effective; several formulations; soluble forms can be incorporated into foods, liquids, and recipes; safe in renal and hepatic disease, pregnancy, geriatrics; can cause gas and bloating. Soluble fiber with low fermentability (i.e., psyllium) is associated with fewer adverse effects such as bloating, flatulence, and abdominal discomfort
Guanylate cyclase-C agonist		
Linaclotide (Linzess)	FDA approved for IBS-C and CIC	Guanylate cyclase-C agonist: Increases fluid secretion and transit time 145- and 290-mcg capsules IBS-C: 290 mcg orally once daily; for CIC: 145 mcg orally once daily Take on empty stomach 30 min before meal; common adverse effects include diarrhea, abdominal pain, flatulence, and abdominal distension; contraindicated in pediatric patients < 6 yr and in mechanical obstruction; avoid in patients 6–17 yr of age; pregnancy category C
Plecanatide (Trulance)	FDA approved for CIC in adults	Guanylate cyclase-C agonist; increases fluid secretion and transit time; 3 mg tablet once daily can be crushed and administered in applesauce or water or via feeding tube; common adverse effect is diarrhea; however, significantly less common than with linaclotide Contraindicated in pediatric patients < 6 yr and in mechanical obstruction; avoid in patients 6–17 yr old
Peripheral opioid antagonist		
Methylnaltrexone (Relistor)	FDA approved for OIC in palliative care patients and for OIC in adult patients with noncancer pain	Peripheral opiate antagonist; will not reverse central analgesia OIC with advanced illness: Subcutaneous injection every other day as needed, dose based on patient weight Onset within 4 hr in about 50% of patients OIC with non cancer pain: Oral tablet 450 mg once daily or 12 mg subcutaneous injection daily

Table 28. Drug Therapy Options for Treatment and Prevention of Constipation *(continued)*

Drugs	Role	Comments
Peripheral opioid antagonist *(continued)*		
Naldemedine (Symproic)	FDA approved for OIC in adult patients with non-cancer-related pain who do not require frequent opioid dose escalation	Peripheral mu-opioid receptor antagonist 0.2 mg once daily Avoid use with strong CYP3A inducers. Monitor for naldemedine toxicity with concomitant moderate and strong CYP3A inhibitors and P-glycoprotein inhibitors
Naloxegol (Movantik)	FDA approved for opioid-induced constipation (OIC) in adult patients with noncancer pain	Peripheral μ-opioid receptor antagonist 12.5- and 25-mg capsules; adjust dose for CrCl < 60 mL/min/1.73 m^2; contraindicated with use of strong CYP3A4 inhibitors or in patients with obstruction
Alvimopan (Entereg)	FDA approved for accelerating gastrointestinal recovery after surgeries that include partial bowel resection with primary anastomosis	Peripheral μ-opioid receptor antagonist 12 mg prior to surgery then 12 mg twice daily until discharge, maximum 7 days (15 doses); long-term use associated with myocardial infarction; only available through a REMS program
Serotonin agonist		
Prucalopride (Motegrity)	FDA approved for treating CIC in adults	Unlike past serotonin agonists (cisapride, tegaserod), prucalopride is highly selective for GI serotonin receptors and has not been reported to result in cardiac adverse effects. Carries a warning for suicidal ideation
Miscellaneous agents		
Docusate sodium Docusate potassium	Prevention of opioid-induced constipation in combination with stimulant laxatives such as senna or prevention of straining in post-MI, postsurgical, and pregnant patients	Onset 1–6 days; requires adequate water intake to be effective
Lubiprostone (Amitiza)	FDA approved for CIC in adults and for IBS-C in women > 18 yr	Chloride channel (ClC-2) activator; results in intestinal fluid secretion; can reduce bloating and abdominal pain; main adverse effect is nausea; dose is 24 mcg twice daily for constipation and 8 mcg twice daily for IBS-C; need negative pregnancy test before use
Tenapanor (Ibsrela)	FDA approved for IBS-C in patients > 18 yr	Tenapanor is a sodium/hydrogen exchanger 3 inhibitor that results in increased intestinal water secretion and GI transit time. Tenapanor may reduce abdominal pain. It is not recommended in patients < 18 yr and is contraindicated in patients < 6 yr because of risks of serious dehydration

CIC = chronic idiopathic constipation; CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; HF = heart failure; IBS-C = constipation-predominant irritable bowel syndrome; MI = myocardial infarction; OIC = opioid-induced constipation; REMS = Risk Evaluation and Mitigation Strategies; STC = slow-transit constipation.

XI. IRRITABLE BOWEL SYNDROME

A. Definition and pathophysiology
   1. IBS is considered a functional GI disorder.
   2. Definition divides IBS into the following subtypes:
      a. Diarrhea predominant (IBS-D)
      b. Constipation predominant (IBS-C)
      c. Mixed IBS (IBS-M): Features of both IBS-D and IBS-C
      d. Unclassified (IBS-U)
   3. The pathophysiology is thought to involve alterations in both CNS and intestinal pain perception, alterations in GI motility and secretion, and contributions from current or past psychosocial factors, gas retention, and possibly previous GI infection or bacterial overgrowth.
      a. IBS is more common in women, lower socioeconomic groups, and patients younger than 50 years.
      b. Patients with IBS have significant reductions in quality of life and use more health care resources.
      c. A comorbid psychiatric illnesses, such as depression or anxiety, may be present in a sizeable percentage of patients with IBS.
   4. Symptoms: In addition to diarrhea or constipation, pain is often a component of all subtypes. Other symptoms (e.g., bloating, distension, spasm, urgency) may be present. These symptoms, together with the Rome IV diagnostic criteria that follow, help distinguish IBS from other functional GI disorders such as CIC.

B. Diagnosis
   1. Diagnosis is made by exclusion. Rule out other GI causes with a thorough workup. Evaluation of a patient's pattern of symptoms may provide insight into subtype, although patients may alternate between forms.
   2. Several diagnostic criteria and scoring systems have been developed, including the Kruis, Manning, and Rome criteria.
      a. The Rome IV criteria are used most commonly and are as follows.
         i. Recurrent abdominal pain, on average, at least one day/week in the last three months, associated with two or more of the following criteria:
            (a) related to defecation
            (b) associated with a change in frequency of stool
            (c) associated with a change in form (appearance) of stool
         ii. Symptoms should have started at least 6 months before diagnosis
      b. Guidelines recommend that if other GI diseases are excluded and no alarm features (e.g., weight loss, bleeding, anemia) are present, diagnosis of IBS can be made with confidence.
      c. The ACG guidelines also recommend:
         i. Screening for celiac disease in patients with IBS-D and IBS-M
         ii. No endoscopy if younger than 50 years and no alarm symptoms
         iii. No routine food allergy testing
         iv. No routine checking for small intestinal bacterial overgrowth unless lactose intolerance is a concern, despite dietary intervention

C. Treatment strategies
   1. Treatment involves a mix of drug, diet, and psychosocial interventions. Cognitive behavioral therapy, dynamic psychotherapy, and hypnotherapy have all shown effectiveness in IBS.
   2. Dietary intervention involves avoidance of foods that trigger symptoms.

3. Drug therapy should target main symptoms and possible psychiatric comorbidities. Combinations of drugs may be necessary for maximal effectiveness. Treatment often begins with nonpharmacologic and nonprescription therapies. Escalation to symptom-driven prescription therapies may be necessary. Choice of treatment should be based on the efficacy of a treatment for a patient's symptoms balanced with the tolerability of the therapy such as the likelihood and severity of adverse effects. Treatment of IBS-M should target the current symptoms.
    a. Antispasmodics: Used mostly for short-term relief of abdominal pain, but also to treat diarrhea in patients with IBS-D. They can be used on an as-needed or scheduled basis. Anticholinergic antispasmodics are contraindicated in patients with comorbid severe UC, GI or urinary obstructions, myasthenia gravis, and glaucoma.
        i. Dicyclomine (Bentyl): Anticholinergic adverse effects
        ii. Hyoscyamine (Levsin, Levsin SL), anticholinergic adverse effects
        iii. Peppermint oil: Use enteric-coated products; it can worsen GERD, but can improve symptoms in IBS and is superior to placebo.
    b. Tricyclic antidepressants: Treat pain, improve global symptoms, and slow motility in patients with IBS-D. They can be used in IBS-C but may worsen constipation
        i. Amitriptyline, nortriptyline, and imipramine are the most studied.
        ii. Doses should not be increased enough to treat comorbid depression.
        iii. Potential for anticholinergic effects, sedation, CV effects, and drug interactions.
    c. Selective serotonin reuptake inhibitors (SSRIs): Treat pain and improve global symptoms similar to the use of tricyclic antidepressants. SSRIs are used for both IBS-D and IBS-C.
        i. Fluoxetine, sertraline, citalopram, and paroxetine are all viable options.
        ii. They tend to have a prokinetic effect; therefore, they can also improve constipation in IBS-C; however, they can also be used for IBS-D, especially if comorbid depression or anxiety exists.
        iii. Adverse effects include insomnia, sexual dysfunction, weight changes, and withdrawal.
    d. Laxatives can be used for IBS-C.
        i. Psyllium has the best evidence; however, it can cause bloating and gas formation. Calcium polycarbophil can be used as an alternative bulk-forming agent. Wheat or corn bran should not be used.
        ii. Polyethylene glycol–based laxatives (MiraLAX) can increase stool frequency, but they have no effect on reductions in abdominal pain and overall symptoms in IBS. There is minimal to no bloating.
        iii. Avoid stimulant laxatives because they can worsen abdominal pain.
    e. Lubiprostone (Amitiza) approved by the FDA for IBS-C in women older than 18 years.
        i. Chloride channel activator; improves motility and possibly pain
        ii. Dose is 8 mcg twice daily with meals for IBS-C.
        iii. Nausea and diarrhea are the main adverse effects.
        iv. Significant cost
    f. Linaclotide (Linzess) is approved for IBS-C.
        ii. Guanylate cyclase-C agonist: increases fluid secretion and decreases transit time
        iii. Dose is 290 mcg orally taken once daily on an empty stomach 30 minutes before meals.
        iv. Common adverse effects: diarrhea, abdominal pain, flatulence, and abdominal distension
    g. Plecanatide (Trulance) is approved for IBS-C.
        i. Structural analog of uroguanylin, an endogenous guanylate cyclase-C agonist, causes an elevation in intracellular cyclic guanosine monophosphate (cGMP), stimulates secretion of chloride and bicarbonate into the intestinal lumen through activation of the cystic fibrosis transmembrane conductance regulator ion channel. Decreased activity of pain-sensing nerves appears to occur because of elevated extracellular cGMP concentration (clinical relevance of the effect on pain fibers has not been established).

   ii. Dose: 3 mg daily without regard to food
   iii. Common adverse effects: Mainly GI related. If severe diarrhea occurs, discontinue plecanatide.
   iv. Counseling points: May be crushed and administered in applesauce or water, or by feeding tube. Dispensed in a monthly blister pack

h. Tegaserod (Zelnorm) is a serotonin-4 partial agonist that is approved by the FDA for IBS-C.
   i. Improves pain, global symptoms, and motility.
   ii. Tegaserod has been approved for reintroduction to the U.S. market for adult women younger than 65 with IBS-C.
   iii. Tegaserod is contraindicated in patients with past myocardial infarction, stroke, transient ischemic attack, or angina. It is also contraindicated in patients with a history of ischemic colitis or other intestinal ischemia.

i. Loperamide: No effects on global symptoms or pain, but reduces motility and increases stool consistency. May be used as an adjunct to other therapies in IBS-D

j. Eluxadoline (Viberzi): (C-IV) FDA approved to treat IBS-D
   i. Mu opioid receptor agonist
   ii. Dose is 100 mg PO twice daily. Reduce to 75 mg PO twice daily if no gall bladder, unable to tolerate 100 mg, concomitant OATP1B1 inhibitor (e.g., cyclosporine, gemfibrozil, antiretrovirals [atazanavir, lopinavir, ritonavir, saquinavir, tipranavir], rifampin, eltrombopag), or mild-moderate hepatic impairment.
   iii. Can cause sphincter of Oddi dysfunction. Contraindications include biliary duct obstruction, alcohol abuse (>3 drinks/day), history of pancreatitis, Child-Turcotte-Pugh class C, severe constipation, or GI obstruction
   iv. Discontinue therapy if constipation lasts for more than 4 days

k. Alosetron (Lotronex): Serotonin-3 antagonist that is approved by the FDA for IBS-D
   i. Improves global symptoms and reduces motility
   ii. Associated with the development of colonic ischemia; therefore, available only through manufacturer prescribing program

l. Probiotics: Some evidence to support improvement in global symptoms, bloating, and flatulence; not enough evidence to recommend specific strains

m. Antibiotics: A short course (10–14 days) of nonabsorbable antibiotic can improve global symptoms of IBS, especially bloating in IBS-D.
   i. Rifaximin 550 mg three times daily for 14 days has FDA approval for IBS-D.
   ii. Limited data with neomycin and metronidazole

Patient Cases

10. A 55-year-old man with a history of chronic alcohol abuse for 25 years is evaluated in the clinic for chronic pancreatitis. For the past 2 months, he has noticed an increase in the frequency of bowel movements to four or five times daily. He describes his stools as foul smelling and slimy. During this time, he has had 14 kg of unintentional weight loss and has intermittent abdominal pain. Quantification of fecal fat indicates an excretion of 20 g every 24 hours. His albumin is 2.1 g/dL, and he weighs 61 kg. He currently takes morphine controlled-release 45 mg twice daily and oxycodone 5–10 mg every 4–6 hours as needed. What is the best course of action for this patient?
    A. Increase MS-Contin to 60 mg twice daily.
    B. Initiate dronabinol to improve appetite.
    C. Initiate pancrelipase 40,000 units per meal.
    D. Add a multivitamin to his regimen.

11. A 32-year-old woman has had intermittent crampy abdominal pain 3–5 days/week, bloating, and reduced frequency of bowel movements for the past 6 months. Before this, she had a bowel movement daily; now, she reports a bowel movement every 2–3 days. She often needs to strain to evacuate her bowels. She reports that her symptoms do not appear related to specific foods. The results of an extensive diagnostic workup are negative, and she is given a diagnosis of IBS-C. She is otherwise healthy and reports no known drug allergies. Which therapeutic intervention is best for this patient?
    A. Amitriptyline 50 mg/day.
    B. Probiotic (i.e., VSL #3) three capsules daily.
    C. Tegaserod 6 mg twice daily.
    D. Lubiprostone 8 mcg twice daily.

12. A 30-year-old woman who is 14 weeks pregnant presents with mild myalgias; a low-grade fever (temperature 99.8°F); four or five loose, watery bowel movements; and one episode of vomiting during the past 18 hours. She reports her 3-year-old daughter and several children in her day care class had the same symptoms 3 days ago. The results of a rapid influenza test are negative, her WBC is 8×10^3 cells/mm^3, and her SCr is 0.9 mg/dL. She takes a prenatal vitamin and reports no known drug allergies. She is given a diagnosis of a presumed viral gastroenteritis. What is the best treatment for this patient's diarrhea?
    A. Loperamide.
    B. Bismuth subsalicylate.
    C. Lactase.
    D. Pyridoxine.

REFERENCES

Gastroesophageal Reflux Disease

1. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-779. doi: 10.1016/S0140-6736(13)60900-9.
2. Haag S, Andrews JM, Katelaris PH, et al. Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. Digestion 2009;80:226-34.
3. Hunt R, Armstrong D, Katelaris P, et al. World Gastroenterology Organisation global guidelines: GERD global perspective on gastroesophageal reflux disease. J Clin Gastroenterol 2017;51:467-78.
4. Katz PO, Gerson LB, Vela MF. Guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterology 2013;108:308-28.
5. Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG Clinical Guideline: Management of dyspepsia. Am J Gastroenterol 2017;112:988-1013.

Peptic Ulcer Disease

1. ACCF/ACG/AHA. 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Circulation 2008;118:1894-909.
2. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. J Am Coll Cardiol 2010;56:2051-66.
3. Chey WD, Leontiadis GI, Howden CW, Moss SF. American College of Gastroenterology Guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112:212-38.
4. Lanza FL, Chan FKL, Quigley EMM, et al. Guidelines for the prevention of NSAID-ulcer complications. Am J Gastroenterol 2009;104:728-38.
5. Wilcox CM, Allison J, Benzuly K, et al. Consensus development conference on the use of non-steroidal anti-inflammatory agents, including cyclooxygenase inhibitors and aspirin. Clin Gastroenterol Hepatol 2006;4:1082-9.

Upper GI Bleeding and SRMD

1. American Society of Health-System Pharmacists (ASHP). Therapeutic guidelines on stress ulcer prophylaxis. Am J Health Syst Pharm 1999;56:347-79.
2. Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the international consensus group. Ann Intern Med 2019;171:805-22.
3. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med 2018;379:2199-208.
4. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012;107:345-60.
5. Worden JC, Hanna KS. Optimizing proton pump inhibitor therapy for treatment of nonvariceal upper gastrointestinal bleeding. Am J Health Syst Pharm 2017;74:109-16.

Inflammatory Bowel Disease

1. AGA Institute Guidelines for the Identification, Assessment and Initial Medical Treatment in Crohn's Disease Clinical Decision Support Tool. Available at http://campaigns.gastro.org/algorithms/IBDCarePathway. Accessed October 30, 2014.
2. American Gastroenterological Association Institute. Technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in Crohn's disease. Gastroenterology 2013;145:1464-78.
3. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. Gastroenterology 2020;158:1450-61.

4. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology 2017;153:827-34.
5. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulizing Crohn's disease. Gut 2014;63:1381-92.
6. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol 2018;113:481-517.
7. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol 2019;114:384-413.5.
8. Talley NJ, Abreu MT, Anchkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol 2011;106:S2-25.
9. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in Crohn's disease. Gastroenterology 2013;145:1459-63.

Complications of Chronic Liver Disease

1. Crabb DW, Im GY, Szabo G, et al. Diagnosis and treatment of alcohol-related liver disease: 2019 practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2020;71:306-33.
2. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2017;65:310-35.
3. Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350 electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA Intern Med 2014;174:1727-1733. doi: 10.1001/jamainternmed.2014.4746.
4. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. 2012. Hepatology 2013;57:1651-3.
5. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. NEJM 1999;34:403-409.
6. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619-28.
7. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease. 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60:715-35.

Viral Hepatitis

1. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org/. Accessed September 13, 2020.
2. Nelson NP, Link-Gelles R, Hofmeister MG, et al. Update: recommendations of the Advisory Committee on Immunization Practices for use of hepatitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for international travel. MMWR Morb Mortal Wkly Rep 2018;67:1216-20.
3. Schille S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on immunization Practices. MMWR Recomm Rep 2018;67:1-31.
4. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASSLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-99.
5. U.S. Public Health Service. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep 2001;50(RR11):1-52.
6. Weinbaum CM1, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57(RR08):1-20.

Nausea and Vomiting

1. American College of Obstetrics and Gynecology (ACOG). Practice bulletin 189: nausea and vomiting of pregnancy. Obstet Gynecol 2018;131:e15-e30.
2. American Gastroenterological Association Institute. AGA technical review on nausea and vomiting. Gastroenterology 2001;120:263-86.
3. Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician 2004;69:1169-74.
4. Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesth Analg 2020;131:411-48.

Pancreatitis

1. Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. Gastroenterology 2018;154:1096-101.
2. Gardner TB, Adler DG, Forsmark CE, et al. ACG clinical guideline: chronic pancreatitis. Am J Gastroenterol 2020;115:322-39.
3. Pham A, Forsmark C. Chronic pancreatitis: review and update of etiology, risk factors, and management. F1000Research 2018;7:607.
4. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis. J Clin Gastroenterol 2005;39:709-16.
5. Waljee AK, Dimagno MJ, Wu BU, et al. Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. Aliment Pharmacol Ther 2009;29:235-46.
6. Witt H, Apte MV, Kiem V, et al. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. Gastroenterology 2007;132:1557-73.

Diarrhea and Constipation

1. Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement: guidelines on constipation. Gastroenterology 2013;144:211-7.
2. Bharucha AE, Pemberton JH, Locke GR. AGA technical review on constipation. Gastroenterology 2013;144:218-38.
3. Ford AC, Moayyaedi P, Lacy BE, et al. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. Am J Gastroenterol 2014;109:S2-26.
4. Ramkumar D, Rao SSC. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroenterol 2005;100:936-71.

Irritable Bowel Syndrome

1. Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol 2018;113:1-18.
2. Ford AC, Moayyaedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014;109:S2-26.
3. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology 2014; 147:1146-8.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Patients receiving PPI therapy for GERD should be reassessed for efficacy. This patient has had some improvement in frequency of symptoms, but they are still not optimally controlled despite lifestyle modifications and being adherent. There is no evidence that upper GI dysmotility is the cause of his GERD symptoms; therefore, adding metoclopramide would not be preferred (Answer A). Switching to an alternative PPI such as omeprazole (Answer C) could be tried, but typically this would be considered in the case of intolerance to another agent. Sucralfate (Answer D) has no role in GERD treatment. The GERD guidelines endorse increasing the PPI frequency to twice daily in patients with continued symptoms, making Answer B correct.

2. Answer: C

The two most common causes of PUD are *H. pylori* infection and NSAID use. This patient has a gastric ulcer with evidence of a clot (indicating recent bleeding) in the setting of NSAID use (aspirin plus ketoprofen). In addition, she is older than 60 years, which is another risk factor for an NSAID-induced ulcer and is probably contributing to her upper GI problems and anemia. The result of the rapid urease test performed on the biopsy specimen is negative, indicating the absence of *H. pylori*. First, the patient should discontinue NSAID use. The use of NSAIDs can markedly delay healing; therefore, NSAID use should be continued only if necessary. Healing of the ulcer should be facilitated by appropriate acid-suppressive therapy. Histamine-2 receptor antagonists, although effective in some instances, are less efficacious in the healing of gastric ulcers than are the PPIs, making Answer A incorrect. Because the patient has tested negative for *H. pylori,* use of an *H. pylori* eradication regimen is not necessary; therefore, Answer B is incorrect. Misoprostol, which is effective in preventing and healing ulcers, is not preferred because of the need for several daily doses, and it is poorly tolerated because of a high incidence of abdominal pain, cramping, and diarrhea; therefore, Answer D is incorrect. The dose should also be at least 600 mcg/day. Proton pump inhibitors are the preferred drugs for healing NSAID-induced ulcers because of their excellent efficacy and favorable adverse effect profile, and they are better tolerated, making Answer C correct.

3. Answer: C

The test-and-treat approach is appropriate in patients with dyspepsia thought to have *H. pylori* infections. Patients older than 45–55 years or those with alarm features should be referred for endoscopic evaluation to rule out the possibility of a more complicated disease. Ambulatory patients can be tested for *H. pylori* using various diagnostic approaches (e.g., UBT). The eradication of *H. pylori* leads to high rates of ulcer healing and minimizes ulcer recurrence. According to treatment guidelines, eradication regimens for *H. pylori* infection should include at least two antibiotics plus an antisecretory agent given for 10–14 days. This can be accomplished with triple-drug therapies containing amoxicillin (or metronidazole) plus clarithromycin in addition to a PPI. Likewise, quadruple therapy with bismuth, tetracycline, metronidazole, and a PPI can be used as a first-line treatment in penicillin-allergic patients or as a second-line treatment of initial failures of triple-drug therapy. This patient requires treatment secondary to a positive test. Answer A would be appropriate if the duration were at least 10 days. Answer B is incorrect because cephalosporins are not recommended in *H. pylori* treatment regimens. Answer D is incorrect because fluoroquinolone-based regimens should be reserved as salvage therapy for patients whose triple and quadruple therapy has failed, and the duration of 21 days is too long. Answer C is correct; quadruple therapy offers similar efficacy and is a viable first-line treatment. Patient adherence should be reinforced to maximize efficacy.

4. Answer: D

Treatment with topical aminosalicylate therapy (e.g., a suppository or enema; Answer D) is a more effective option for patients with mildly active UC with distal disease than are oral therapies (e.g., balsalazide; Answer A). Methotrexate (Answer B) has a limited role in maintaining corticosteroid-induced remission in patients with CD, but not UC. Infliximab (Answer C) would be indicated for moderate-severe UC.

5. Answer: B

This patient has moderate to severe CD involving the terminal ileum and colon. Mesalamine (Answer A), though well tolerated, is minimally effective in CD and

would not be indicated for moderate to severe disease. Budesonide (Answer C) is effective in mild-moderate CD affecting the terminal ileum and proximal colon; therefore, the disease severity and location of the disease would not fit this regimen. Adalimumab (Answer D) would be appropriate, but the dose is for maintenance and would need to be 160 mg initially for induction. Combining infliximab and azathioprine (Answer B) has been shown to result in the highest rates of remission in moderate to severe CD compared with the use of either agent alone.

6. Answer: C

Patients with cirrhosis and ascites are at risk of developing SBP, an infection of the ascitic fluid usually caused by an enteric gram-negative organism. Typical signs of infection include fever, abdominal pain, nausea, and rebound tenderness. Diagnosis is made according to clinical symptoms plus laboratory evidence. The laboratory diagnosis is by paracentesis, with identification of more than 250/mm^3 neutrophils (polymorphonuclear neutrophils) in the ascitic fluid. This patient's value is 450/mm^3. If clinical and laboratory signs and symptoms are present, antibiotic therapy directed against enteric gram-negative bacteria should be initiated immediately (Answer A). Third-generation cephalosporins such as cefotaxime and ceftriaxone are preferred (Answer C). Aminoglycosides should be avoided because of their potential to cause nephrotoxicity (Answer B). Vancomycin should be reserved for resistant gram-positive organisms (Answer B). In addition to antibiotic therapy, the use of intravenous albumin reduces the incidence of renal failure and improves in-hospital and 30-day mortality; it is indicated given that the patient's SCr is greater than 1.0 mg/dL and her BUN is greater than 30 mg/dL. The use of oral antibiotics to treat acute SBP is not well studied (Answer D); however, an oral regimen (e.g., norfloxacin or trimethoprim/sulfamethoxazole daily) should be instituted and continued indefinitely after recovery to reduce the incidence of subsequent infections.

7. Answer: B

Management of overt hepatic encephalopathy should initially involve removal and treatment of precipitating factors and the use of therapies aimed at reducing ammonia concentration. Recent guidelines recommend the use of lactulose (Answer B) to rapidly reduce ammonia concentrations in the short term. Therapy can also be continued as prophylaxis against subsequent episodes, if needed. Nonabsorbable antibiotics such as rifaximin can be used, but rifaximin 550 mg twice daily (Answer A) is indicated for use in the prevention of recurrent hepatic encephalopathy and is effective when combined with lactulose. Ceftriaxone (Answer D), which would not be as effective as rifaximin, is indicated in patients with cirrhosis who present with upper GI bleeding. Although polyethylene glycol 3350 (Answer C) has shown some efficacy in the treatment of hepatic encephalopathy, the dose used in recent trials was 4 L administered over 4 hours.

8. Answer: B

This patient has a chronic HBV infection, given the elevations in ALT and AST, the presence of HBsAg, and the high concentrations of circulating HBV DNA. The patient also has evidence of severe necroinflammation on biopsy. The patient has HBeAg positivity, and a YMDD mutation is present. She appears to have compensated liver disease, given her albumin concentration, INR, and lack of ascites or encephalopathy. Given her persistently elevated liver function test results, biopsy results, and high viral load, she should receive treatment (Answer A is incorrect). Treatment with an oral reverse transcriptase inhibitor is preferred first-line therapy. Because the patient has a lamivudine-resistant organism, as evidenced by the YMDD mutation, lamivudine therapy would be ineffective (Answer C is incorrect), and a drug therapy that treats lamivudine-resistant pathogens (e.g., tenofovir or entecavir) is recommended initially. Because the patient has an elevated SCr of 1.9 mg/dL, tenofovir alafenamide is preferred to tenofovir disoproxil fumarate (Answer D is incorrect). Entecavir is a preferred agent with activity against lamivudine-resistant virus. Entecavir is also preferred for patients with compromised renal function and would be the best choice of those listed (Answer B is correct).

9. Answer: B

This patient has newly diagnosed chronic HCV infection. He has compensated cirrhosis and is treatment naive. He qualifies for the currently recommended simplified treatment regimens. Patients with genotypes 1–6 with compensated cirrhosis should receive either glecaprevir 300 mg/pibrentasvir 120 mg for 8 weeks or sofosbuvir

400 mg/velpatasvir 100 mg for 12 weeks. Patients with genotype 3 require additional resistance testing before using the sofosbuvir/velpatasvir regimen. This patient has genotype 1a; therefore, initiating glecaprevir/pibrentasvir would be most appropriate at this time (Answer B is correct). Withholding therapy (Answer A) would not be optimal because the current guidelines recommend treatment for all patients with chronic HCV, except for those with a short life expectancy whose condition would not be altered by HCV treatment. Ledipasvir and sofosbuvir (Answer C) were previously recommended as first-line therapy for patients with genotype 1a. However, the current guidelines favor pan-genotypic regimens as first line. The combination of pegylated interferon, ribavirin, and sofosbuvir (Answer D) was previously recommended, but direct-acting agents are now preferred, and pegylated interferon–based therapies are no longer recommended.

10. Answer: C

This patient has signs and symptoms of maldigestion and malabsorption secondary to the loss of pancreatic exocrine function. This is manifested by the presence of steatorrhea, weight loss, and an elevated fecal fat concentration. Management should include replacement of exogenous pancreatic enzymes to facilitate nutrient digestion and absorption (Answer C). Oral pancrelipase products are pork derived and contain lipase, amylase, and protease. A typical starting dose for an adult patient should deliver 40,000–50,000 lipase units per meal, with titration based on reduction in steatorrhea and evidence of weight gain. Although chronic abdominal pain is a typical symptom of chronic pancreatitis, increasing the patient's morphine dose will not help with the symptoms related to the lack of enzymes (Answer A). Likewise, using appetite stimulants such as dronabinol will not be beneficial if enzyme therapy is not initiated (Answer B). Finally, this patient is malnourished, and a multivitamin would be beneficial; however, patients with chronic pancreatitis may need extra supplementation of fat-soluble vitamins after enzyme therapy is initiated and increased caloric intake to facilitate weight gain (Answer D).

11. Answer: D

This patient meets the criteria for IBS-C on the basis of a negative diagnostic workup and the presence of abdominal pain, bloating, and constipation for more than 3 months. Drug therapy should target the predominant symptoms. The agents most beneficial in IBS-C are bulk-forming laxatives, which improve the frequency of bowel movements and can reduce bloating, and SSRIs, which provide relief from abdominal pain, improve global symptoms of IBS, and improve motility in most patients. The tricyclic antidepressants have effects similar to the SSRIs but are associated with anticholinergic effects, which may worsen constipation. Thus, amitriptyline would not be preferred in this case (Answer A). Lubiprostone is approved for IBS-C in women older than 18 years and improves motility and possibly abdominal pain (Answer D). It is the best choice presented, given the patient's symptoms. Probiotics such as VSL #3 can improve global symptoms of IBS, but they would not improve bowel frequency; therefore, use would be best with another therapy that would increase stool frequency (Answer B). Although effective for IBS-C when it was available, tegaserod is available only on an emergency basis because of its association with the development of CV events (Answer C).

12. Answer: A

Diarrhea is caused by a variety of conditions, with viral pathogens being one of the most common causes. This patient probably developed diarrhea through contact with her daughter, who is in day care and had similar symptoms a few days earlier. In addition, her low-grade fever, myalgias, watery diarrhea, and vomiting point to a potential viral cause. Although most episodes of viral gastroenteritis are self-limited, symptomatic relief may be necessary to prevent dehydration. Antidiarrheal therapy should be selected according to patient preference and the presence of any precautions or contraindications. If this patient desires therapy, a therapy should be chosen that minimizes risk to the patient and the fetus, given that she is pregnant. Loperamide (Answer A) is an effective agent for short-term relief of diarrhea, and it carries an FDA pregnancy category B rating; therefore, it would be the best choice in this case. Use of bismuth (Answer B), although effective, should be avoided in pregnant and nursing patients because of the risk of potential toxicity. Lactase (Answer C) would be indicated only if the patient's diarrhea were secondary to lactose intolerance. Pyridoxine (Answer D) is used for the treatment and prevention of nausea and vomiting in pregnancy, but it has no effect on the treatment of diarrhea related to viral gastroenteritis.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

This patient has signs of dysphagia, an alarm symptom that is sometimes associated with a more complicated case of GERD. The patient has tried antacids with minimal relief and has a history of NSAID use. The patient is older than 45 years, which increases his risk of developing gastric cancer. Therefore, he should be referred for endoscopic evaluation to rule out a more complicated disease (Answer B). Using either H_2RAs (Answer A) or a PPI as initial therapy after endoscopic evaluation would be appropriate if the patient does not respond to antacids; however, a twice-daily dosing of PPIs (Answer C) is not necessary as initial dosing. Changing medications that reduce LES tone (e.g., calcium channel antagonists) is an appropriate recommendation for reducing GERD symptoms; this should be considered after invasive testing is performed (Answer D).

2. Answer: C

For patients beginning long-term NSAID therapy, a thorough assessment of patient- or drug-related factors that may predispose them to the development of GI toxicity is necessary. Likewise, an evaluation of the patient's level of CV risk is necessary. Given the use of low-dose aspirin for preventing CV events, this patient would be considered at high risk of CV events. Efforts to avoid GI toxicity should include the use of the GI agent that is least toxic at the lowest effective therapeutic dose. A GI-protective agent should be considered to minimize NSAID-induced erosions and ulcers. Indomethacin (Answer B) and piroxicam (Answer D) are more likely to cause GI complications than is naproxen (Answer C). Use of COX-2 inhibitors (Answer A) is acceptable in patients with rheumatoid arthritis because these agents reduce GI complications and effectively treat pain. However, this patient has CV risk factors including diabetes, hypertension, and dyslipidemia. Recent findings of increased CV events, especially with high doses of COX-2 inhibitors, would preclude their use. Therapy with an acid-suppressive agent is also an acceptable choice for GI prevention in users of nonselective NSAIDs. Proton pump inhibitors are effective for this indication (Answer C). The H_2RAs are ineffective in preventing serious NSAID-induced GI complications (Answer B). Misoprostol, although effective, is associated with a high incidence of diarrhea and abdominal pain and the need for multiple daily dosing (Answer D). Given that this patient is considered at moderate risk of GI complications, because of the patient's use of aspirin and need for high-dose NSAIDs, the use of naproxen plus a PPI would be preferred, according to the recent ACG guidelines (Answer C).

3. Answer: D

This patient presents with signs and symptoms consistent with an NSAID-induced upper GI bleed. He has several risk factors for NSAID-induced GI bleeding, including age older than 60 years, use of aspirin, and long duration of NSAID use. The presence of underlying CV disease, although not a direct risk factor, may also contribute to increases in NSAID GI toxicity. He also has many criteria that place him at high risk of rebleeding. According to the consensus recommendations for nonvariceal bleeding, he should receive an intravenous PPI by bolus and subsequent continuous infusion for 72 hours (Answer D). Note that the guidelines provided state that this therapeutic approach can be extrapolated to patients with NSAID-induced ulcers and bleeding, even though most of the data included in the guidelines pertain to non–NSAID-induced causes of upper GI bleeding. He will then require treatment with an appropriate dose of an oral PPI for at least 8 weeks; after that, he should be assessed for possible continued prophylactic use. H2RAs (Answer A) are less efficacious for the treatment and prevention of rebleeding for NSAID-induced ulcers. Sucralfate (Answer B) has minimal efficacy in the setting of acute GI bleeding. Oral PPIs (Answer C) are effective in preventing and healing NSAID-induced ulcers; however, in this case, the lansoprazole dose is inadequate for treatment. Oral PPIs should be used at an appropriate dose after intravenous therapy.

4. Answer: D

Given this patient's presenting symptoms, she would be classified in the mild active disease category. First-line therapy for active extensive disease would consist of an oral aminosalicylate at a dose equivalent to mesalamine at least 2 g/day. A product such as Delzicol (Answer D) is formulated to release mesalamine in the colon, which would be appropriate in this case. Sulfasalazine

(Answer A) has reported efficacy for this indication and is activated in the colon; however, this patient reports a life-threatening allergy to sulfonamide-containing medications. Topical therapy with hydrocortisone enema (Answer B) would be appropriate if the patient had disease distal to the splenic flexure. Immune modulators such as mercaptopurine (Answer C) have a long onset of action (3–15 months) and are not appropriate for acute active disease.

5. Answer: B

Primary prophylaxis of bleeding should be instituted in patients with large varices and cirrhosis. Nonselective β-blockers are appropriate as first-line therapy. Therapy should be targeted to achieve a resting heart rate of 55 beats/minute or a 25% reduction from baseline. The patient has taken propranolol for 1 month and has not met these goals (Answer A). Because he is tolerating propranolol, the dose should be increased (Answer B), and he should be observed to reassess the need for further dosage adjustments. Adding a nitrate (Answer C) would increase the reduction in portal pressures; however, nitrates have not been shown to improve mortality. Most patients have an increased risk of adverse effects with this combination. Nonselective β-blockers are preferred to cardioselective agents (Answer D) because antagonism of the β-receptor prevents splanchnic vasodilation.

6. Answer: C

The sensitivity of a test can be thought of as the proportion of patients with a disease who have a positive test, whereas specificity deals with the proportion of patients without the disease who have a negative test. Calculating these values is accomplished by establishing a 2 × 2 table representing the results of the test. The sensitivity can be calculated by dividing the number of patients having the disease using the new test who were also positive using a gold standard test (true positives), which in this case is 850, by the number of patients receiving a diagnosis of having the disease using the gold standard, which in this case is 900. The 900 represents the true positives and 50 patients with the disease but without the diagnosis of it, according to the new test (false negatives). Specificity can be calculated by taking the number of patients not having the disease using the gold standard who tested negative with the new test (true negatives = 85). Next, divide this result by the number of patients who truly had no disease using the gold standard, 100, which incorporates the 15 patients who tested positive with the new test but truly had no disease (i.e., false positives). Sensitivity = 850/(850 + 50) = 94%; specificity = 85/(85 + 15) = 85%. (Answer C). The other numerical manipulations possible are not representative of sensitivity and specificity (Answers A, B, and D).

Result	Infection	No Infection	Total
Positive	850	15	865
Negative	50	85	135
Total	900	100	1000

7. Answer: C

Postexposure therapy for HAV may be offered to restaurant patrons if a food handler at a restaurant is documented to have HAV and is considered infectious while handling food. The most effective therapies for postexposure prophylaxis are administration of HAV immune globulin or vaccine. The efficacy of the vaccine approaches that of immune globulin, but only in patients younger than 40 years, according to the Centers for Disease Control and Prevention guidelines. The period for administration should be within 14 days of exposure; therefore, this patient does not meet the criteria for receiving HAV immune globulin (Answer B) or vaccine (Answer A). She should be observed for signs and symptoms of active disease (Answer C). Hepatitis A vaccine should be offered to patients as preexposure therapy if they are considered at risk of exposure to HAV. The combination of vaccine and immune globulin for postexposure therapy is unnecessary (Answer D).

8. Answer: C

This patient presents with elevated aminotransferases, consistent with alcoholic hepatitis. Prognosis of alcoholic hepatitis can be initially evaluated with the Maddrey discriminant function (MDF) score, calculated as 4.6 × (Patient's PT − Control PT) + Total bilirubin (mg/dL), where *PT* is prothrombin time. Patients whose score is greater than 32 are believed to have a poor prognosis. This patient's MDF score is 42.5; therefore, she would qualify for treatment with a 4-week course of prednisolone 40 mg/day, followed by a 2-week taper (Answer C). This can lead to a 30% decrease in the risk ratio of short-term death. Naproxen (Answer A), though having anti-inflammatory activity, has no role in the treatment of alcoholic hepatitis and may precipitate acute kidney injury in patients with

liver disease; therefore, it should be avoided. Octreotide (Answer B) would be indicated in the setting of acute variceal bleeding, and midodrine (Answer D) is indicated for hepatorenal syndrome. This patient has no evidence of either condition.

9. Answer: D

The treatment used in this case for chronic HCV, genotype 3 with compensated cirrhosis and NS5A resistance-associated substitutions is the fixed-dose combination of sofosbuvir 400 mg/velpatasvir 100 mg with the addition of ribavirin. Alternatively, sofosbuvir/velpatasvir/voxilaprevir may be considered. Genotype 2 responds well to therapy. Although this patient appears to be responding to treatment, as indicated by reductions in aminotransferases and HCV RNA, the earliest that HCV RNA should be evaluated is 4 weeks, not 2 weeks (Answer A). This patient does not appear to have adverse effects to sofosbuvir (Answer B) or symptoms consistent with extrahepatic manifestations of HCV (e.g., glomerulonephritis or rheumatologic disorders; Answer C). The patient does have evidence of hemolysis, including scleral icterus, rapid decline in hematocrit, fatigue, and elevated indirect bilirubin, probably representing hemolytic anemia secondary to ribavirin, which commonly occurs within the first 2 weeks of therapy (Answer D). Furthermore, there is no evidence that the decrease in hematocrit is secondary to bleeding.

10. Answer: A

Infliximab is an appropriate agent for the treatment of fistulizing CD. Because of its effects on TNF, latent infections such as tuberculosis can become reactivated during therapy. Therefore, patients should have a purified protein derivative or QuantiFERON-TB test to rule out underlying tubercular disease before treatment is initiated (Answer A). Although infliximab therapy is associated with infusion-related reactions, administering a test dose is not routinely recommended (Answer B). Infliximab may be administered in a clinic setting; it does not require admission to the hospital for monitoring (Answer C). Infliximab therapy is associated with exacerbations of underlying heart failure and is contraindicated in patients with New York Heart Association class III or IV disease. This patient is young, with no history of heart failure and no clinical signs of heart failure. Therefore, a baseline echocardiogram is not necessary to assess cardiac function (Answer D).

11. Answer: C

Treatment of nausea and vomiting in medical inpatients can be accomplished by administering a variety of antiemetics. Nausea and vomiting are common symptoms associated with pyelonephritis, and they will subside once appropriate antibiotic therapy adequately treats the infection. However, patients will need symptomatic relief until the antibiotics take effect. Agents typically used for medical inpatients include phenothiazines and serotonin antagonists. The use of intravenous or rectal formulations is usually preferred for patients with severe nausea, such as this patient. Ondansetron (Answer C) is a serotonin antagonist that can be administered as needed intravenously and is effective in treating nausea caused by a variety of medical conditions. Despite its effects on serotonin, it should not cause any significant interaction with the patient's sertraline dose. Prochlorperazine (Answer A), a commonly used antiemetic, would be a viable option; however, using the oral product in this case would not be preferred, given that the patient has severe vomiting. In addition, prochlorperazine is a dopamine antagonist, and the patient is receiving a high dose of risperidone. This combination can lead to the development of EPS and, in severe cases, QTc prolongation. Metoclopramide (Answer B) is typically used as an antiemetic when gastroparesis is present or as an adjunctive therapy for patients whose other therapies have failed. Metoclopramide also has dopamine antagonist effects that can lead to the development of EPS. Diphenhydramine (Answer D) is more effective for nausea related to motion sickness, but it would not effectively treat severe short-term nausea or the other options.

12. Answer: B

This patient presents with acute constipation given his symptoms of abdominal pain, both by complaints and on examination; reduced frequency of bowel movements; and radiographic evidence of a large quantity of stool in the colon. Contributing factors include the use of verapamil and oxycodone without the use of a drug regimen to prevent constipation. Therapy should be instituted to provide a quick onset to initiate a bowel movement and provide symptom relief. Saline laxatives such as sodium phosphate (Answer A) provide quick results, especially when given by enema. The oral formulation of sodium phosphate results in phosphate absorption and is problematic in patients with chronic kidney disease. This patient's CrCl is about 34 mL/

minute/1.73 m^2, so saline laxatives should be avoided. Bisacodyl suppositories (Answer B) provide rapid stimulation of the lower intestinal tract without the risk of electrolyte absorption, so they would be preferred in this case. Methylcellulose (Answer C) is a bulk-forming laxative that would not treat the patient's acute constipation, but it would be an option for preventing constipation on a long-term basis in this patient once the short-term episode is resolved. Although methylnaltrexone (Answer D) is indicated for opioid-induced constipation, it would generally not be used as first-line agent, given the need for injection and the added cost compared with traditional laxatives.

13. Answer: D

Stress-related mucosal disease develops in critically ill patients and can lead to significant upper GI bleeding. Therapy initiation to prevent SRMD is based on the presence of risk factors. Independent risk factors include mechanical ventilation and coagulopathy. This patient is currently receiving mechanical ventilation and has other risk factors such as sepsis, hypotension, and acute renal insufficiency; therefore, he would meet the criteria for initiating pharmacologic prophylaxis. Both H_2RAs and PPIs are viable first-line options. Cimetidine (Answer C) carries an FDA-approved indication for the prevention of SRMD; however, the dosing provided is incorrect because 50 mg/hour is the approved dose. Likewise, cimetidine would need to be dose adjusted for the patient's CrCl, which can be assumed less than 10 mL/minute/1.73 m^2. Pantoprazole (Answer D) would be a better choice in this case, and it does not require adjustment for the CrCl. Sucralfate (Answer A) has historically been used to prevent SRMD, but it has fallen out of favor because of the need for multiple daily dosing and the risk of aluminum accumulation in patients with kidney disease. Antacids such as magnesium hydroxide (Answer B) are not as effective as H_2RAs, require multiple daily dosing, and are associated with electrolyte accumulation in patients with kidney injury.

14. Answer: D

Several different forms of bias exist that can adversely affect the validity or results of a trial. Errors in sampling or measurement, incorrect patient enrollment methods, and differences in patient populations studied in a trial are examples of areas of study design and conduction that may introduce bias. When evaluating drug literature, an important aspect of deciding whether the reported results are valid is to recognize important causes of bias. A retrospective cohort design typically uses medical records to evaluate events that occurred in the past after exposure to a drug. Recall bias (Answer A) pertains to study outcomes or events that patients are asked to recall, with results differing depending on the ability of patients to remember an event. For this study, objective documentation of ulceration or bleeding was performed to make comparisons between groups, eliminating patient recall as a potential bias. Misclassification bias (Answer B) is typically problematic in case-control studies, in which patients can be entered in the case study group but have not actually been exposed to the drug in question, which would not be applicable in this case. Interviewer bias (Answer C), or observer bias, is typically problematic in direct patient survey studies; it pertains to variation in the way different investigators collect data within a trial. To eliminate this bias, everyone involved in data collection in a study should be trained in the same manner of data collection to maintain consistency. Again, because an objective measure of GI toxicity was recorded by endoscopy, the possibility of interviewer bias is minimized. Channeling bias (Answer D) is a form of allocation bias in which medications with similar therapeutic indications are administered to patients with differing prognoses or risk levels. Should claims be made that a new drug introduced to a therapeutic class has a particular advantage—in this case, a safer GI toxicity profile—the chance that use will be channeled to high-risk patients is much greater. Given that the drug may be studied in higher-risk patients rather than those in the comparator group, the development of more events in this newer drug group may mask potential differences in safety and cause these events to be attributed to drug-induced toxicity.

15. Answer: B

Positive predictive value gives the proportion of patients with a disease when the presence of the disease is indicated by a diagnostic test. It is affected by disease prevalence; thus, as disease prevalence falls, so does the positive predictive value of the test. Using the sensitivity, specificity, and prevalence, a 2 × 2 table can be constructed. The positive predictive value is calculated by dividing the true positives by the sum of the true and false positives. In this case, that would be 190/(190 + 24) × 100 = 89% (Answer B). The total number of patients who tested positive divided by the number

who tested negative, 75% (Answer A), does not indicate the positive predictive value of a test. Specificity deals with the proportion of patients without the disease who have a negative test result; it can be calculated by taking the number of patients not having the disease using the gold standard who tested negative with the new test (true negatives = 276). Next, divide this by the number of patients who truly had no disease using the gold standard, 300, which incorporates the 24 patients who tested positive with the new test but truly had no disease (i.e., false positives). Specificity = 276/(276 + 24) = 92% (Answer C). The number of patients who tested negative and had no infection divided by the total number of patients with no infection does not illustrate positive predictive value 276/(276 + 10) = 96% (Answer D).

Result	Infection	No Infection	Total
Positive	190	24	214
Negative	10	276	286
Total	200	300	500

Geriatrics

Mary M. Bridgeman, Pharm.D., BCPS, BCGP

Ernest Mario School of Pharmacy
Rutgers, The State University of New Jersey
Piscataway, New Jersey

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Mary M. Bridgeman, Pharm.D., BCPS, BCGP

Ernest Mario School of Pharmacy
Rutgers, The State University of New Jersey
Piscataway, New Jersey

Learning Objectives

1. Evaluate the pharmacotherapeutic regimens of older adults to support optimal risk and benefit of medications.
2. Assess inappropriate medication prescribing in older adults using accepted tools.
3. Recommend appropriate pharmacotherapy for patients with dementia, including appropriate interventions for patients with behavioral and psychological symptoms of dementia (BPSD).
4. Recommend appropriate treatment for urinary incontinence and benign prostatic hyperplasia (BPH).
5. Evaluate the risks and benefits, safety, and efficacy of medication classes used in the treatment of rheumatoid arthritis, osteoarthritis, and gout.

Abbreviations in This Chapter

AD	Alzheimer's disease
ADLs	Activities of daily living
AUASI	American Urological Association Symptom Index
BPH	Benign prostatic hyperplasia
BPSD	Behavioral and psychological symptoms of dementia
CI	Cholinesterase inhibitor
DMARD	Disease-modifying antirheumatic drug
IADL	Instrumental activities of daily living
LUTS	Lower urinary tract symptoms
MCI	Mild cognitive impairment
MMSE	Mini–Mental State Examination
OA	Osteoarthritis
PSA	Prostate-specific antigen
PVR	Postvoid residual
RA	Rheumatoid arthritis
RF	Rheumatoid factor
TNF	Tumor necrosis factor
UI	Urinary incontinence
ULT	Urate-lowering therapy
XOI	Xanthine oxidase inhibitor

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.

An 85-year-old man presents to the primary care clinic 1 month after the death of his spouse. His medical history is significant for hypertension, hyperlipidemia, benign prostatic hyperplasia (BPH), and major depressive disorder. His current medications include lisinopril 10 mg daily, atorvastatin 20 mg daily, tamsulosin 0.4 mg daily, diazepam 5 mg at bedtime as needed for sleep, and escitalopram 10 mg daily. His daughter reports that he has been more lethargic and unsteady walking during the past 3 days. The patient reports trouble sleeping, necessitating the use of diazepam every night this past week. His blood pressure is 135/72 mm Hg and heart rate is 76 beats/minute. Urinalysis is unremarkable, thyroid-stimulating hormone (TSH) is within the reference range, and Geriatric Depression Scale score is 6/15.

1. Which medication is most contributing to this patient's lethargy and confusion?
   A. Diazepam.
   B. Lisinopril.
   C. Atorvastatin.
   D. Escitalopram.

2. Which age-related change in pharmacokinetics most likely underlies this patient's medication-related problem?
   A. Delayed oral absorption.
   B. Decreased renal excretion.
   C. Slowed metabolism in the liver.
   D. Decreased volume of distribution.

Questions 3 and 4 pertain to the following case.

A 76-year-old woman was recently admitted to a long-term care facility for rehabilitation after several falls at home. Her medical history is significant for hypertension, hypothyroidism, Alzheimer disease (AD), hyperlipidemia, and osteoarthritis (OA). She takes metoprolol succinate 50 mg daily, levothyroxine 75 mcg daily, atorvastatin 10 mg daily, and donepezil 10 mg daily. Her blood pressure is 126/80 mm Hg and heart rate is 66 beats/minute. Basic metabolic panel results are all within reference ranges; 25-hydroxyvitamin D

concentration is 20 ng/mL, TSH is 1.89 mU/L, total cholesterol is 180 mg/dL, low-density lipoprotein cholesterol is 140 mg/dL, high-density lipoprotein cholesterol is 35 mg/dL, and triglycerides is 176 mg/dL. Her Mini–Mental State Examination (MMSE) score is 16/30, and her Geriatric Depression Scale score is 2/15.

3. Which recommendation would be most appropriate to reduce this patient's risk of falls?
   A. Begin memantine titration.
   B. Initiate vitamin D 1000 units daily.
   C. Decrease metoprolol succinate to 25 mg daily.
   D. Initiate calcium carbonate 500 mg twice daily.

4. Which would be most appropriate for the patient's osteoarthritic knee pain?
   A. Ibuprofen 200 mg four times daily.
   B. Acetaminophen 650 mg three times daily.
   C. Tramadol 50 mg three times daily as needed for pain.
   D. Hydrocodone/acetaminophen 5/325 mg every 4 hours as needed for pain.

Questions 5–7 pertain to the following case.
An 80-year-old woman presents to your clinic accompanied by her daughter, who no longer feels comfortable leaving her mother alone because of her mother's "increasing forgetfulness." The patient's medical history is significant for type 2 diabetes, hypertension, coronary artery disease, congestive heart failure, and OA. She takes the following medications: acetaminophen 650 mg every 6 hours as needed for pain, lisinopril 20 mg daily, furosemide 20 mg daily, potassium chloride 20 mEq daily, carvedilol 12.5 mg twice daily, and glipizide 5 mg daily. Her MMSE score is 18/30. Blood tests obtained last week showed a normal basic metabolic panel, except for a fasting plasma glucose reading of 65 mg/dL. Her hemoglobin A1C (A1C) is 5.6%. A urinalysis is unremarkable. No nutritional deficiencies are noted. The patient's blood pressure is 130/80 mm Hg and heart rate is 60 beats/minute. She receives a diagnosis of AD.

5. Which initial intervention would be most appropriate to help with this patient's cognitive function?
   A. Donepezil 10 mg daily.
   B. Galantamine extended release (ER) 24 mg daily.
   C. Memantine 10 mg twice daily.
   D. Rivastigmine patch 4.6 mg daily.

6. Which intervention would be most appropriate to prevent an adverse drug reaction?
   A. Discontinue glipizide.
   B. Discontinue lisinopril.
   C. Reduce carvedilol to 6.25 mg twice daily.
   D. Reduce potassium chloride to 10 mEq daily.

7. One year later, the patient returns to the clinic. She has moved in with her daughter. Lately, she wanders around the house continuously. She often changes clothes, cries out, and asks repetitive questions. Her current medication regimen includes donepezil 10 mg daily, which she has been taking for the past 6 months. Which would be most appropriate for this patient's new behavioral symptoms?
   A. Initiate olanzapine 5 mg daily.
   B. Initiate risperidone 0.5 mg twice daily.
   C. Change the donepezil dosage to 23 mg daily.
   D. Change acetaminophen to 650 mg every 6 hours around-the-clock.

8. An 80-year-old woman had a total right knee replacement 3 days ago after conservative strategies for OA failed. Her medical history is significant for hypothyroidism, osteoporosis, OA, and hyperlipidemia. Her current medications include simvastatin 20 mg daily, risedronate 35 mg weekly, levothyroxine 75 mcg daily, and oxycodone/acetaminophen 5/325 mg 1 tablet every 4 hours as needed for moderate pain. She is in the hospital preparing for discharge. As the pharmacist is counseling the patient on her discharge medication, the patient reports a new onset of "losing her water" the day before and again overnight. Which intervention would be most appropriate for this patient?
   A. Urinalysis.
   B. Pelvic floor exercises.
   C. Tolterodine 2 mg daily.
   D. Duloxetine 20 mg daily.

Questions 9 and 10 pertain to the following case.
A 69-year-old man is admitted to the hospital after a motorcycle collision. He had serious injuries resulting in a left leg above-the-knee amputation and has undergone several surgical procedures and rehabilitation in the past 2 weeks. His current medications include tamsulosin 0.4 mg daily, atenolol 25 mg daily, amlodipine 10 mg daily, senna/docusate 8.6/50 mg twice daily, oxycodone controlled release 10 mg every 12 hours, and hydromorphone 4 mg every 3 hours as needed for breakthrough pain (uses 1–2 daily). His blood pressure is 155/88 mm Hg, heart rate is 84 beats/minute, and postvoid residual (PVR) volume is 400 mL after voiding 110 mL. His chronic medical conditions are unremarkable except for hypertension, BPH, and gastroesophageal reflux disease.

9. Which intervention would be most appropriate for this patient?
   A. Change tamsulosin to alfuzosin 10 mg once daily.
   B. Increase atenolol to 50 mg daily.
   C. Change tamsulosin to terazosin 5 mg daily.
   D. Reduce hydromorphone to 2 mg every 3 hours as needed for breakthrough pain.

10. One year later, the patient has pain caused by OA of his right knee. His current medications are amlodipine 10 mg daily, acetaminophen 1000 mg three times daily, omeprazole 40 mg daily, and aspirin 81 mg daily, together with treatment for his BPH. Which agent would be best to initiate for this patient's knee pain?
   A. Celecoxib 200 mg daily
   B. Naproxen 500 mg twice daily
   C. Diclofenac 1% gel apply 4 g to knee every 6 hours.
   D. Methylprednisolone 40 mg injected into affected joint.

11. A 72-year-old woman (height 66 inches, weight 82 kg) whose medical history is significant for rheumatoid arthritis (RA), type 2 diabetes, gastroesophageal reflux disease, and hypothyroidism presents to the clinic with inflammation of the joints of the hands and stiffness lasting 1–2 hours in the morning. She is a smoker. Her current medications include pantoprazole 40 mg daily, metformin 850 mg twice daily, levothyroxine 100 mcg daily, folic acid 1 mg daily, methotrexate 12.5 mg weekly, naproxen 500 mg twice daily, calcium 600 mg twice daily, and vitamin D 1000 units twice daily. Her laboratory tests show a negative rheumatoid factor (RF) but positive anti–cyclic citrullinated peptides. The physician determines that this is a flare of moderate disease. Which would be the most appropriate intervention for maintenance treatment of this patient's RA?
   A. Change naproxen to prednisone 20 mg daily.
   B. Change methotrexate to 25 mg intramuscularly.
   C. Change methotrexate to leflunomide 20 mg daily.
   D. Add sulfasalazine 500 mg twice daily and hydroxychloroquine 400 mg daily.

12. A 66-year-old man is initiated on allopurinol 100 mg once daily and naproxen 500 mg twice daily for the treatment of an acute gout flare. On diagnosis, no tophi were present, serum urate was 10.9 mg/dL, and GFR was 78 mL/minute/1.73 m^2. His allopurinol dose is increased 2 weeks after initial presentation to 200 mg, and at his 1-month follow-up, the allopurinol dose was further increased to 300 mg once daily. Naproxen was discontinued because his symptoms had resolved; serum urate was 8.7 mg/dL and GFR was 84 mL/minute/1.73 m^2. He is seen 2 weeks later for an emergency follow-up because he has developed a new rash; serum urate is 7.4 mg/dL and GFR is 72 mL/minute/1.73 m^2. Which is best for managing his gout at this time?
   A. Increasing allopurinol to 400 mg daily.
   B. Reinitiating naproxen 500 mg twice daily.
   C. Changing allopurinol to febuxostat 40 mg daily.
   D. Changing allopurinol to pegloticase 8 mg intravenously every 2 weeks.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient–specific Pharmacotherapy
    a. Tasks 1, 3, 4
    b. Systems and Patient-Care Problems:
        i. Dementia
        ii. Behavioral Symptoms of Dementia
        iii. Urinary Incontinence
        iv. Benign Prostatic Hyperplasia
        v. Arthritis
        vi. Osteoarthritis
        vii. Rheumatoid Arthritis
        viii. Gout

I. OPTIMIZING PHARMACOTHERAPY IN OLDER ADULTS

A. Aging

1. Aging is a normal process whereby the human body declines after peak growth and development. In general, aging results as the body responds to environmental stressors according to the person's health and lifestyle factors together with genetic makeup. If environmental stressors are severe enough or individuals have too small a reserve capacity, aging causes frailty, disability, and increased vulnerability to disease and death.
2. At present, 52 million or 16% (U.S. Census Bureau, 2018) of Americans are 65 or older. This figure is projected to rise to 95 million or 23% by 2060. Older adults constitute about 16% of the population, but they are responsible for:
   a. 34% of medication costs
   b. 36% of hospital stays
   c. 40% of medication-related hospitalizations
   d. 50% of medication-related deaths
3. At least $30 billion/year is spent on medication-related morbidity.
4. There is large heterogeneity in older adults: Diversity is increasing, and incomes have a wide range; some people live independently into their 90s and beyond, whereas others become frail and dependent at a younger age. Measurement of aging with years of life is insensitive to the differences between older adults.
   a. If an individual survives to age 65, he or she will likely live an additional 13–20 years.
   b. If an individual survives to age 85, he or she will likely live an additional 6–7 years.

B. Pharmacokinetic Changes Associated with Aging

1. Common physiologic changes occur in most older adults, but they are highly variable because of differences in genetics, lifestyle, and environment.

Table 1. Common Physiologic Changes with Age That May Change Drug Pharmacokinetics

Organ System	Physiologic Change with Aging	Effect on Pharmacokinetics
GI	↑ Or no change in stomach pH ↓ GI blood flow Slowed gastric emptying Slowed GI transit	• ↓ Absorption of some drugs and nutrients requiring acid environment • Absorption rate may be prolonged
Skin	Thinning of dermis Loss of subcutaneous fat	• ↓ Or no change to drug reservoir formation with transdermal formulation
Body composition	↓ Total body water ↓ Lean body mass ↑ Body fat ↓ Or unchanged serum albumin ↑ α_1-Acid glycoprotein	• ↑ Volume of distribution and accumulation of lipid-soluble drugs • ↓ Volume of distribution of water-soluble drugs • ↑ Free fraction of highly protein-bound drugs
Liver	↓ Liver mass ↓ Blood flow to the liver ↓ Or no change in CYP enzymes	• ↓ First-pass extraction and metabolism • ↑ Half-life and • ↓ clearance of drugs with a high first-pass extraction and metabolism • ↓ Or no change in phase I metabolism • No change in phase II drug metabolism
Renal	↓ GFR ↓ Renal blood flow ↓ Tubular secretion ↓ Renal mass	• ↓ Renal elimination of many medications • ↑ Half-life of renally eliminated drugs and metabolites

CYP = cytochrome P450; GFR = glomerular filtration rate; GI = gastrointestinal.

2. Absorption
    a. Iron, vitamin B_{12}, antifungals, and calcium are decreased with hypochlorhydria or achlorhydria.
    b. Slower gastric emptying may increase the risk of ulceration from aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, or potassium chloride tablets.
    c. Most drugs are absorbed by passive diffusion without significant age-related changes.
    d. Transdermal formulations usually require a subcutaneous fat layer to form a drug reservoir for absorption. Use with caution in patients who are thin or cachectic.
3. Distribution
    a. Lipid-soluble medications, such as diazepam, have an increased half-life in older adults.
    b. Highly albumin-bound drugs such as phenytoin may have a larger fraction of free (active) drug.
    c. P-glycoprotein, an efflux transporter for several organs including the brain, decreases with aging, which may lead to higher brain concentrations of medications. One example is opioid analgesics.
4. Metabolism
    a. Morphine and propranolol clearance are substantially reduced because of a reduction in first-pass metabolism. Expect other drugs with high first-pass metabolism to be affected similarly.
    b. Changes in metabolism through phase I (oxidative) reactions catalyzed by cytochrome P450 (CYP) enzymes are variable and confounded by age, sex, concomitant drugs, and genetics.
    c. Lorazepam, oxazepam, and temazepam depend solely on phase II metabolism and are less affected by age-related changes in metabolism.
5. Elimination
    a. Drugs eliminated through glomerular filtration must be dosed according to individual estimated renal function. Chronic medication examples can be found in the 2019 American Geriatrics Society (AGS) Beers Criteria.
    b. The Cockcroft-Gault equation is a validated method to estimate creatinine clearance (CrCl) for drug dosing in older adults. Note the exceptions (e.g., dabigatran, dofetilide, rivaroxaban) that used actual body weight in the Cockcroft-Gault equation, rather than ideal body weight during drug development, which is reflected in the labeled dosing.
    c. The National Kidney Foundation recommends using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009) to estimate glomerular filtration rate. However, this recommendation has not been validated in older adults.

Table 2. Differences in Renal Estimation with Common Formulas

Patient: 85-year-old person with an SCr of 1 mg/dL	**Cockcroft-Gault CrCl (mL/min/1.73 m^2)**	**MDRD Estimated GFR (mL/min/1.73 m^2)**	**CKD-EPI CrCl (mL/min/1.73 m^2)**
64-inch-tall white woman weighing 60 kg	39	56	51 (stage 3)
64-inch-tall African American woman weighing 60 kg	39	68	60 (stage 2)
70-inch-tall white man weighing 75 kg	57	75	68 (stage 2)
70-inch-tall African American man weighing 75 kg	57	91	79 (stage 2)
Cockcroft-Gault: CrCl = [(140 − age) × ideal body weight in kg]/[(72 × SCr)] × 0.85 if female (use actual weight if it is less than ideal body weight)			
MDRD: Estimated GFR = $186 \times SCr^{1.154} \times age^{-0.203} \times 1.21$ if black × 0.742 if female			
CKD-EPI Creatinine Equation 2009[a]: CKD-EPI equation expressed as a single equation: GFR = $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]			

[a]SCr is standardized SCr in milligrams per deciliter; κ is 0.7 for women and 0.9 for men, α is –0.329 for women and –0.411 for men, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; MDRD = Modification of Diet in Renal Disease.

d. Some clinicians round the serum creatinine concentration (SCr) up to 1 mg/dL because older adults have lower muscle mass, which produces less creatinine, and an extremely low SCr would overestimate renal function with these formulas. This rounding is not supported by evidence and remains controversial. In addition, clinicians may use adjusted weight for patients with obesity with formulas used for younger adults, though evidence in older adults is lacking.

C. Pharmacodynamic Changes Common with Aging
   1. Increased sensitivity
      a. Benzodiazepines and opioids: Increased sensitivity to the central nervous system (CNS) effects
      b. Antipsychotics, metoclopramide: Extrapyramidal effects and tardive dyskinesia
      c. Tricyclic antidepressants, α-blockers, antihypertensives: Orthostatic hypotension
      d. Warfarin: Greater inhibition of synthesis of vitamin K–dependent clotting factors; increased risk of bleeding
      e. NSAIDs: Gastrointestinal (GI) bleeding
      f. Anticholinergic agents: Increased risk of confusion, dry mouth, constipation, other adverse effects
   2. Decreased sensitivity
      a. β-Blockers
      b. β-Agonists
   3. Impaired homeostasis
      a. Diuretics, angiotensin-converting enzyme inhibitors: Sodium and electrolytes
      b. Diuretics: Hydration status

Patient Case

Questions 1 and 2 pertain to the following case.

An 85-year-old woman (weight 65 kg) who resides at home with her daughter has a medical history significant for type 2 diabetes and hypertension, and 1 year ago, she had a right hip fracture after a fall. Her regularly scheduled medications include glyburide 10 mg daily, lisinopril 10 mg daily, metformin 500 mg twice daily, aspirin 81 mg daily, and a multivitamin daily. Her as-needed medications include melatonin 6 mg at bedtime as needed for sleep, meclizine 25 mg ½ tablet three times daily as needed for dizziness, and docusate 100 mg twice daily. Her laboratory results show fasting plasma glucose 90 mg/dL, sodium (Na) 138 mEq/L, potassium (K) 4.5 mEq/L, chloride (Cl) 102 mEq/L, carbon dioxide (CO_2) 25 mEq/L, blood urea nitrogen (BUN) 30 mg/dL, SCr 1.8 mg/dL, and TSH 4.0 mU/L.

1. Considering the potential for altered pharmacokinetics, which set of medications is most likely to cause problems for the patient?
   A. Aspirin and melatonin.
   B. Lisinopril and meclizine.
   C. Lisinopril and metformin.
   D. Glyburide and metformin.

2. Considering the potential for increased pharmacodynamic sensitivity, which set of medications is most likely to cause problems for the patient?
   A. Aspirin and melatonin.
   B. Lisinopril and meclizine.
   C. Lisinopril and metformin.
   D. Glyburide and metformin.

D. Optimal Pharmacotherapy in Older Adults
   1. In an optimal pharmacotherapeutic regimen, the benefit of the therapy outweighs the risk of adverse effects.
   2. To reduce risk, doses of many medications must be adjusted in older adults because of age-associated changes in drug pharmacokinetics and pharmacodynamics.
   3. Alternative medications may be more appropriate because of these changes.
   4. Therapeutic window becomes smaller even with dose and drug adjustments.

E. Drug-Related Risk Assessment for Older Adults
   1. Overuse of medications
      a. Unnecessary drugs: Use of more medications than clinically indicated and unneeded therapeutic duplication
      b. Common unnecessary drugs: GI agents, CNS agents, vitamins, minerals
      c. May be caused by
         i. Prescribing cascade: When a drug is prescribed for treating another drug's adverse effects
         ii. Several prescribers
         iii. Care transitions
   2. Underuse of medications
      a. Omitted but necessary or indicated drug therapy or inadequate dosing
      b. Commonly underused drugs: Anticoagulants, statins, antihypertensives
      c. Medications considered appropriate according to guidelines may be omitted because prescriber or patient is overly wary of adverse drug effects.
   3. Nonadherence
      a. Unintentional nonadherence caused by complex drug regimen
      b. Dementia or other cognitive impairment increases risk.
      c. Cost of medications is another barrier.
      d. Intentional nonadherence because of patient health beliefs or concerns
   4. Withdrawal syndromes
      a. Abrupt discontinuation of medication may cause rebound symptoms or delirium.
      b. Common culprits: Antihypertensives, antidepressants, anxiolytics, pain medications
   5. Inappropriate medications
      a. Explicit tools commonly used to identify for quality measures; objective statements that do not require clinical judgment for interpretation. Best known is the AGS Beers Criteria for Potentially Inappropriate Medications. Alternative medications to the potentially inappropriate agents listed in this guideline are also available from AGS.
         i. Evidence-based list of drugs likely to cause problems
         ii. Adopted by many federal agencies and Part D plans
         iii. Arranged as drugs and drug classes to avoid, drugs to avoid in certain diseases or conditions, and drugs to be used with caution
         iv. Examples: Anticholinergics, benzodiazepines, sedative-hypnotics, older antipsychotics, certain opioids or pain medications, hypoglycemics, NSAIDs, and GI drugs
         v. Another tool popular in European countries is the screening tool of older people's prescriptions and screening tool to alert to right treatment (STOPP/START) criteria.
      b. Implicit tools are patient-centered, take more time to apply; interpretation requires clinical judgment and patient-specific information. Best studied is the Medication Appropriateness Index, also FORTA (fit for the aged) criteria
         i. 10 questions to ask about each medication regarding indication, effect, dosing, directions, interactions, duration, and cost
         ii. Indication, effectiveness, and correct dosage carry the most weight.

6. Choosing Wisely criteria
    a. 10 things to question in older adults
    b. 7 of the 10 items are drug related.
        i. Antipsychotics in patients with dementia should be avoided.
        ii. Target A1C in diabetes management is 7.5% or higher.
        iii. Avoid benzodiazepines and sedative-hypnotics for insomnia, agitation, or delirium.
        iv. Do not initiate antimicrobials for bacteriuria without symptoms.
        v. Assess benefit-risk of cholinesterase inhibitors (CIs).
        vi. Appetite stimulants are not helpful for anorexia or cachexia.
        vii. Drug regimen review is necessary with every new prescription.

Patient Case

Questions 3–5 pertain to the following case.

A 70-year-old woman (height 66 inches, weight 71.7 kg [158 lb]) is in the clinic for an evaluation by the clinical pharmacist for polypharmacy. She has complaints of fatigue, light-headedness, constipation, and "too many medicines." Her medical history is significant for hypertension, coronary artery disease (drug-eluting stent 8 years ago), chronic obstructive pulmonary disease, diabetes mellitus, incontinence, frequent urinary tract infections, depression, and moderate dementia. Vital signs include blood pressure 160/82 mm Hg, heart rate 51 beats/minute, respiratory rate 16 breaths/minute, and oxygen saturation 99% on room air. Her current medications are as follows: fluticasone/salmeterol 250/50 1 puff twice daily, aspirin 81 mg daily, acetaminophen 650 mg three times daily, clopidogrel 75 mg daily, donepezil 10 mg daily, glipizide 5 mg twice daily, lisinopril 10 mg daily, loratadine 10 mg daily, metoprolol 50 mg twice daily, paroxetine 40 mg daily, ranitidine 150 mg twice daily, simvastatin 40 mg at bedtime, and tolterodine 2 mg at bedtime. Nitrofurantoin 100 mg twice daily for 10 days was initiated 3 days ago. Laboratory values from her physician visit 3 days before are as follows: Na 130 mg/dL, K 4.2 mEq/dL, Cl 99 mg/dL, CO_2 24 mEq/dL, BUN 24 mg/dL, SCr 1.6 mg/dL, fasting glucose 67 mg/dL, A1C 6.3%, urinalysis unremarkable except for blood- small, pH 7.5, RBC 11–25/high-power field (HPF), white blood cells 0–2/HPF, and bacteria 168/HPF.

3. Which medication list best depicts the medications with the greatest potential to harm this patient, according to the AGS 2019 Beers Criteria?
    A. Paroxetine, donepezil, tolterodine.
    B. Donepezil, glipizide, simvastatin.
    C. Glipizide, donepezil, nitrofurantoin.
    D. Metoprolol, clopidogrel, ranitidine.

4. Given the available patient information, which set of medications is least appropriate for this patient, according to the Medication Appropriateness Index?
    A. Fluticasone/salmeterol, ranitidine, donepezil, tolterodine.
    B. Metoprolol, clopidogrel, ranitidine.
    C. Aspirin, glipizide, donepezil, nitrofurantoin.
    D. Paroxetine, nitrofurantoin, simvastatin.

5. Which medications would best be discontinued, according to the Choosing Wisely criteria?
    A. Paroxetine, ranitidine, donepezil, tolterodine.
    B. Metoprolol, clopidogrel, ranitidine.
    C. Glipizide, donepezil, nitrofurantoin.
    D. Ranitidine, nitrofurantoin, glipizide, tolterodine.

F. Changes in Function Associated with Aging
   1. Quality of life, place of residence, and social and physical function may become more important than duration of life.
   2. Instrumental activities of daily living (IADLs)
      a. Examples: Doing housekeeping, using telephone, managing medications, shopping, cooking, managing money
      b. Need to do these to live independently
   3. Activities of daily living (ADLs)
      a. Examples: Feeding, dressing, bathing, toileting, transferring
      b. Nursing home or home caregivers are required if ADLs cannot be performed.
   4. Cognitive screening
      a. Mini-Mental State Examination (MMSE; copyright protected, requires permission and fee to use)
      b. Montreal Cognitive Assessment
      c. SLUMS (St. Louis University Mental Status) examination
   5. Mood: Geriatric Depression Scale
   6. Gait and balance: Timed "Up and Go," Berg Balance Scale
   7. Drugs can alter cognition, mood, and mobility.

G. Geriatric Syndromes
   1. Geriatric syndromes follow a concentric model, with many risk factors and several etiologies contributing to a clinical presentation rather than the linear model with one etiology following a defined pathogenesis.
   2. Falls
      a. Possible etiologies: Psychoactive medications, polypharmacy, orthostatic hypotension, hypoglycemia, hyponatremia, myocardial infarction, urinary tract infection
      b. Examples of contributing risk factors: Vitamin D deficiency, poor balance, deconditioning/muscle weakness, poor vision, environment
      c. STEADI falls program, available from the CDC (https://www.cdc.gov/steadi/index.html), contains materials for patients and providers to improve awareness and mitigate risk.
   3. Delirium
      a. Possible etiologies: Psychoactive medications, polypharmacy, hypoglycemia, hyponatremia, myocardial infarction, urinary tract infection
      b. Example of contributing risk factors: Dementia, stroke, vitamin B_{12} deficiency, poor hearing, lack of sleep
   4. Hazards of hospitalization
      a. Usual aging involves a decline in several organ systems, which are further compromised when an older patient is admitted to the hospital and expected to remain in bed.
         i. Immobilization leads to deconditioning. Regaining what was lost takes longer in older adults.
         ii. Immobilization and inability to obtain water lead to decreased plasma volume, which can lead to syncope, falls, and fractures.
         iii. Sensory deprivation from isolation and lack of glasses or hearing aids can lead to delirium, which may require treatment with both nonpharmacologic and pharmacologic interventions, including restraints or antipsychotics.
         iv. Immobilization and "tethers" (e.g., intravenous lines, oxygen lines, catheters) necessitate nursing assistance to bathroom. Unavoidable delay may lead to incontinence, catheters, infections, falls, and pressure sores.
         v. Prescribed diets or nothing-by-mouth status leads to dehydration, malnutrition, insertion of feeding tubes, and aspiration pneumonia.

b. Preventable adverse drug events are common contributors to increased morbidity and mortality in older hospitalized adults.
c. Functional decline typically follows a hospitalization and is called a "cascade to dependency."
d. One study showed that subjects with a loss of ADLs at discharge had a higher mortality rate (40% at 12 months), with only 30% returning to baseline function.
e. Early mobility, adequate nutrition, reduced polypharmacy, and early discharge planning may reduce functional disability and length of stay.

Patient Case

Questions 6 and 7 pertain to the following case.

A 70-year-old woman is admitted to the hospital with a broken arm after a fall. While in the hospital, she is on bedrest most of the time, loses 2 kg (current weight 63 kg), and has trouble sleeping. She is to be discharged to a rehabilitation facility for 2–3 weeks of therapy. Her medications at discharge are glipizide 5 mg daily, lisinopril 10 mg daily, aspirin 81 mg daily, a multivitamin daily, mirtazapine 15 mg at bedtime, calcium 500 mg twice daily, and tramadol 25 mg every 8 hours as needed for pain.

6. When recommending medication changes for this patient, which functional assessment is most important to evaluate?
   A. IADLs.
   B. Depression.
   C. Pressure sores.
   D. Gait and balance.

7. To maintain and improve function in this patient, which intervention is best to implement?
   A. Add atorvastatin 10 mg daily.
   B. Increase lisinopril to 20 mg daily.
   C. Add vitamin D 1000 units twice daily.
   D. Change tramadol to naproxen 500 mg twice daily as needed for pain.

II. DEMENTIA

A. Epidemiology
   1. Affects 4–5 million people in the United States
   2. Of people 65 years and older, 6% have dementia, increasing to 30%–50% of those 85 years and older.

B. Dementia Definition: Cognitive decline in complex attention, executive function, learning and memory, language, and/or perceptual–motor or social cognition AND interferes with work or social functions
   1. Delirium should be ruled out first.
      a. Delirium: A disturbance in attention and awareness developing over hours to days with fluctuation during the day
      b. Delirium is a geriatric syndrome, with age, underlying dementia, functional impairment, and medical comorbidities as risk factors.
      c. Etiologies include medications such as sedative-hypnotics, antidepressants, anticholinergics, opioids, anticonvulsants, and antiparkinson drugs.
   2. Mild cognitive impairment (MCI) is used to describe the condition of people with some deficits in cognition who do not meet the criteria for dementia.
   3. AD is the most common type of dementia.

4. Theories of pathogenesis include cholinergic, β-amyloid plaques, tau protein (neurofibrillary tangles), genetics (apolipoprotein E4), and inflammation (cytokines, prion).
5. Several other types of dementia exist; few are reversible.

Table 3. Comparisons of Memory Impairment and Dementias with AD

Disease	Differences from AD	Treatment Notes
Common Irreversible Causes		
MCI	No interference with work or social functions 1 in 5 progress to AD	Eliminate or control risk factors for dementia May use CIs, which reduced risk of progression by 40% in one study
Vascular dementia	Includes focal neurological signs and symptoms Radiologic evidence of stroke Onset within 3–6 mo of stroke Abrupt deterioration followed by stepwise progression	Control of cardiac and vascular risk factors CIs and memantine not effective
Lewy body dementia	Fluctuating cognition with pronounced variation in attention and alertness Recurrent visual hallucinations Motor features of PD	Especially avoid typical antipsychotics, which may worsen motor symptoms May use CIs
Dementia of advanced PD	PD onset predates cognitive impairment Usually at latter stages of PD	Especially avoid typical antipsychotics, which may worsen motor symptoms May use CIs
Frontotemporal dementia	Affects personality, behavior, self-care, and language Onset in ages 45–65 with a 2- to 10-yr course	CIs may worsen behavior and cause agitation SSRIs or trazodone may be beneficial
Reversible Causes		
Vitamin B_{12} deficiency	Progressive memory loss Vitamin B_{12} serum concentration < 300 pg/mL May be anemic also, but folic acid may disguise the anemia	Replace vitamin B_{12} according to standard protocols
Hypothyroidism	Deficient or inadequate replacement of thyroxine	Levothyroxine replacement according to standard protocols
Depression	Trouble concentrating and memory Apathy and "I don't care" responses	Treatment of depression according to standard protocols
NPH	Triad of progressive memory loss, incontinence, and gait abnormality Symptoms improve after lumbar puncture	Surgical placement of ventricular shunt

AD = Alzheimer's disease; CI = cholinesterase inhibitor; MCI = mild cognitive impairment; NPH = normal pressure hydrocephalus; PD = Parkinson disease; SSRI = selective serotonin reuptake inhibitor.

C. Assessment Tools
   1. MMSE
      a. 30-point scale; higher score indicates better function
      b. Untreated AD: Score usually decreases 3 or 4 points a year.
      c. Heavily relies on verbal and language skills, so less accurate if education is poor
   2. SLUMS examination
      a. 30-point scale; higher score indicates better function
      b. Includes adjustment of scores for lower educational status

3. Montreal Cognitive Assessment
    a. 30-point scale; higher score indicates better function
    b. Less reliant on verbal or language skills
4. Mini-Cog assessment
    a. 5-point scale; higher score indicates better function
    b. Easiest to administer; takes 3 minutes

D. New Diagnostic Guidelines
1. Recognizes three phases
    a. Preclinical, asymptomatic phase
    b. Symptomatic, predementia phase (MCI)
    c. Dementia phase
2. Diagnosis may be identified for research purposes by:
    a. Biomarkers of increased tau or decreased β-amyloid concentrations in cerebrospinal fluid
    b. Reduced glucose uptake in brain on positron emission tomography scanning using florbetapir F 18 or flutemetamol F 18
    c. Atrophy of specific brain areas on magnetic resonance imaging
3. Preclinical and predementia phases are targets for investigational studies to halt progression.
4. For clinicians, diagnosis is given without these biomarkers or imaging.

E. Clinical Presentation and Classification

Table 4. Stages of AD

	MMSE (out of 30)	**Examples of Cognitive Loss**	**Examples of Functional Loss**
Mild	20–24	Some short-term memory loss; word-finding problems	Loss of IADLs such as laundry, housekeeping, and managing medications; may get lost in familiar places
Moderate	10–19	Disorientation to time and place, inability to engage in activities and conversation	Needs assistance with ADLs such as bathing, dressing, and toileting
Severe	< 10	Loss of speech and ambulation, incontinence of bowel and bladder	Dependency in basic ADLs such as feeding oneself; often needs around-the-clock care

ADLs = activities of daily living; IADLs = instrumental activities of daily living; MMSE = Mini–Mental State Examination.

F. Management
1. Goals are to maintain function and cognition.
    a. Functional management and safety issues
    b. Legal considerations
2. Nonpharmacologic therapy
    a. Education, especially with caregiver
    b. Physical exercise and mental exercise
    c. Management of comorbid conditions
    d. Avoid alcohol and medications that worsen mentation.
3. Medical foods:
    a. Caprylidene; L-methylfolate/methylcobalamin/acetylcysteine; phosphatidylserine/docosahexaenoic acid/eicosapentaenoic acid; and omega-3 fatty acids/uridine/choline/vitamins C, E, B_6, and B_{12}/selenium/folic acid
    b. Intended to support metabolic balance in the brain, lipid imbalances, or synaptic integrity, respectively

Patient Case

8. An 84-year-old widow lives at home alone. She can perform ADLs and most IADLs with her daughter's assistance. Her current medications are hydrochlorothiazide 12.5 mg daily for hypertension, tolterodine long acting 4 mg daily for incontinence, escitalopram 20 mg daily for depression, acetaminophen 650 mg as needed for arthritis, and calcium/vitamin D for prevention of osteoporosis. The patient's physician administers the MMSE, and her score is 23/30. On physical examination, no cogwheel rigidity or tremor is noted. Which recommendation would be best at this time?

   A. Add donepezil 5 mg daily.

   B. Discontinue tolterodine and reassess the patient.

   C. Add vitamin B_{12} 1000-mg injection monthly.

   D. Change hydrochlorothiazide to lisinopril 5 mg daily.

4. Pharmacologic therapy

Table 5. Comparison of Drugs for AD Treatment

Drug	Starting Dose	Maintenance Dose	Dosage Forms	Pharmacologic Properties	Comments
Cholinesterase Inhibitors					
Donepezil	5 mg daily	10 mg daily May increase to 23 mg/day	Tablets Orally disintegrating tablets	Acetylcholinesterase inhibitor; metabolized in part by CYP2D6 and CYP3A4 Protein binding 96%	Labeled for mild to moderate and moderate to severe AD
Rivastigmine	1.5 mg twice daily 4.6-mg patch daily	3–6 mg twice daily 9.5-mg patch daily; may increase to 13.3-mg patch daily	Capsules Oral solution Transdermal patch	Acetyl- and butyryl-cholinesterase inhibitor Nausea, vomiting, and diarrhea seem more intense than with other CIs	Labeled for mild to moderate and moderate to severe AD as well as mild to moderate dementia with Parkinson disease Skin reactions with patch
Galantamine	4 mg twice daily	8–12 mg twice daily 8–24 mg ER once daily	Tablets Oral solution ER capsules	Selective competitive, reversible acetylcholinesterase inhibitor and nicotine receptor modulator Metabolized in part by CYP2D6 and CYP3A4	Labeled for mild to moderate AD dementia Preferable to administer with food Renal dosing adjustment necessary
Glutamatergic Therapy					
Memantine	5 mg once daily 7 mg ER once daily	10 mg twice daily 28 mg ER once daily	Tablets Oral solution ER capsules	*N*-methyl-D-aspartate receptor antagonist that blocks glutamate transmission	Labeled for moderate to severe AD; may be used in combination with acetylcholinesterase inhibitors
Combination Product					
Donepezil/memantine	10/28 mg once daily in the evening	10/28 mg once daily	ER capsule	Acetylcholinesterase inhibitor and *N*-methyl-D-aspartate receptor antagonist	Use after stabilized on donepezil and memantine separately Renal dosing adjustment necessary

ER = extended release.

a. Adverse effects of CIs
    i. GI: Nausea, vomiting, diarrhea, elevated risk of GI bleeding
    ii. CNS: Headache, insomnia, dizziness
    iii. Cardiac: Bradycardia, orthostatic hypotension, syncope (AGS Beers Criteria note CIs as inappropriate drugs in patients with syncope)
    iv. Genitourinary: Incontinence
    v. Long-term adverse effects: Anorexia, weight loss, falls, hip fracture, pacemaker placement
b. Adverse effects of memantine: Agitation, urinary incontinence (UI), insomnia, diarrhea, dizziness, confusion, headache

5. Summary of consensus treatment guideline recommendations, American Psychiatric Association, American College of Physicians, and American Academy of Family Physicians, 2007–2008
    a. Initiate a CI in patients with mild to moderate AD.
    b. No evidence one agent is superior to others
    c. Titrate to recommended maintenance dose as tolerated.
    d. May increase to maximum dose if tolerated and maintenance dose no longer effective, but clinically meaningful improvement unlikely
    e. In moderate to severe disease, may use a CI, memantine, or both a CI and memantine
    f. Slight or no benefit with combination therapy in systematic reviews
    g. Studies find no benefit of memantine in mild AD.
6. Controversy over clinical significance of responses

Table 6. Evidence for Response to Drugs for AD

Drug	Test	Testing Range	Response Difference Compared with Placebo	
			Mean	Range
CI	AD Assessment Scale–Cognitive	0–70	–2.7	–2.73 to –2.01
Memantine	Severe Impairment Battery	0–100	2.97	1.68–4.26

7. Therapy duration
    a. In general, need 3–6 months to evaluate for objective benefit with tools
    b. There are limited studies investigating long-term efficacy beyond 1 year, but many receive the drug for years.
    c. The Choosing Wisely criteria recommend evaluating at 12 weeks and considering discontinuation if the goals of therapy are not met.
    d. In general, discontinue at advanced stages of disease. Tapering is recommended if the patient is taking a high dose.
    e. Some rebound agitation may occur.
8. Herbals and dietary supplements
    a. Vitamin E was not shown effective in most large prospective trials. A recent randomized controlled trial of 613 veterans with mild to moderate AD using 2000 international units/day over 2 years showed a delay in clinical progression of 19% per year.
    b. Gingko biloba was not effective in prevention or treatment in randomized controlled trials.
    c. Observational studies support the effect of the Mediterranean diet, exercise, and curcumin (turmeric).

Patient Cases

9. An 87-year-old man with AD receives rivastigmine 6 mg twice daily. His family notes improved functional ability but reports that he has nausea and vomiting that appear to be related to rivastigmine. Which recommendation is best for the patient at this time?

   A. Advise the patient to take rivastigmine with an antacid.

   B. Change rivastigmine to the patch that delivers 9.5 mg daily.

   C. Discontinue rivastigmine and initiate memantine 5 mg twice daily.

   D. Add prochlorperazine 25 mg by rectal suppository with each rivastigmine dose.

10. A 75-year-old woman with AD who lives at home with her husband has been treated with donepezil 10 mg daily for about 3 years. When she began therapy, her MMSE score was 21/30; her present MMSE score is 17/30. The patient cannot perform most IADLs but can perform most ADLs with cueing. About 2 months ago, her donepezil dose was increased to 23 mg, but she could not tolerate it, and it was reduced back to 10 mg daily. Her husband asks about changing her drug treatment to help maintain her function. Which is the next best course of action?

   A. Retry donepezil 23 mg daily.

   B. Initiate memantine 5 mg daily.

   C. Add vitamin E 400 units twice daily.

   D. Change donepezil to rivastigmine 9.5-mg patch daily.

III. BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

A. Epidemiology

1. As disease progresses from mild to moderate, behavioral and psychological symptoms of dementia (BPSD) occur. These tend to wane as the disease progresses to severe.
2. Up to 90% of patients with dementia have BPSD at some point in disease progression.
3. Associated with high rate of disability, functional decline, poor health outcomes, physical injury, nursing home placement, and emergency services
4. Behaviors commonly peak during late afternoon or early evening and are thus called "sundowning."

Table 7. Symptoms During Disease Progression

MMSE Score	Stage	Symptoms	
25	Mild	• Memory loss	• Mood swings[a]
20		• Apathy	• Mild executive dysfunction
		• Poor drawing	• Mild personality changes[a]
15	Moderate	• Unable to learn	• Aggression, psychosis[a]
10		• Aphasia, apraxia	• Confusion, insomnia[a]
		• Wandering, agitation[a]	• Need ADL assistance
5	Severe	• Gait changes[a]	• Loss of ADLs
0		• Incontinence	• Confined to bed

[a]Noncognitive symptoms.

B. Assessment
   1. Scales are rarely used in nursing home or clinical practice, but it is important to identify the target behavior, how often it is occurring, and how severe it is in order to assess the treatment response.
   2. Assess for a medical reason that may precipitate the target behavior and treat it, if found.
      a. Pain is a common issue that patients cannot communicate. Treat with scheduled acetaminophen.
      b. Delirium precipitated by medical illness or medication should be ruled out.

C. Nonpharmacologic Treatment: Cornerstone of Therapy
   1. The theory is that behavior is the communication of unmet need.
   2. Eliminate antecedents and triggers.
   3. Person-centered interventions: Consider long-standing habits, values, and beliefs of patient; use distraction, music, aromatherapy, and pet therapy.
   4. Symptoms likely to respond: Wandering, hoarding, hiding objects, repetitive questioning, withdrawal, social inappropriateness, apathy

D. Pharmacologic Treatment: None of these are U.S. Food and Drug Administration (FDA)-labeled indications.
   1. Agency for Healthcare Research and Quality has published a summary on the use of atypical antipsychotic agents for off-label indications. Atypical antipsychotics improve behavioral symptoms of dementia, but effect sizes are small and adverse effects are significant.
   2. Retrospective case-control study of older veterans with dementia during a 180-day period indicates haloperidol number needed to harm (NNH) = 8, compared with atypical antipsychotics with NNH = 14–31 for risk of death
   3. Antipsychotic medications may increase the risk of death when used in older adult patients with dementia-related psychosis (black box warning).

Table 8. Drug Treatment for BPSD

Symptom	Presentation	Treatment Options After Nonpharmacologic Efforts Ineffective
Anxiety	Part of this is because they cannot remember things	Buspirone or SSRI/SNRI or gabapentin Limit benzodiazepines
Apathy	One of the earliest symptoms Nonpharmacologic treatment tailored to patient's activities	CIs Methylphenidate effective in small, short-term studies
Depression	Up to 80% of patients with AD have depression	SSRI or mirtazapine
Insomnia	Sleep-wake cycle is disrupted	Melatonin
Wandering	Walk so much they begin to lose weight	No drug will stop patients from wandering
Paranoia, hallucinations, sundowning	They may think because they cannot find something, you stole it Often accuse spouse of infidelity If psychosis and delusions do not bother anyone, do not use drugs	Risperidone, olanzapine, quetiapine, and aripiprazole have been tried. Use very low doses. ADEs may offset any benefit
Aggression, resistance to care	Most difficult and best response is to treat nonpharmacologically	Drugs under investigation for agitation include prazosin, dextromethorphan/quinidine, and citalopram

ADE = adverse drug effect; BPSD = behavioral and psychological symptoms of dementia; SNRI = serotonin-norepinephrine reuptake inhibitor.

Patient Case

Questions 11 and 12 pertain to the following case.

11. You are evaluating the medication profile of an 87-year-old woman who resides in a secure advanced dementia unit. Her medical history includes dementia (likely AD), Parkinson disease, and OA. She needs assistance with all ADLs, including total assistance with bathing and dressing, as well as help with feeding. She transfers with minimal help to a wheelchair. Her medication regimen includes donepezil 10 mg daily, memantine 10 mg twice daily, carbidopa/levodopa 25/100 mg four times daily, and a multivitamin supplement daily. The patient's most recent MMSE score is 5/30. When reviewing the nursing notes, you see several references to the patient's continuously crying out, "Help me, help me," beginning around 5 p.m. On medical evaluation, reversible causes of her hypervocalization are ruled out. Which initial approach is most appropriate for this patient?
    A. Initiate ibuprofen 400 mg every 8 hours.
    B. Order haloperidol 1 mg every 6 hours as needed for agitation.
    C. Begin music therapy with songs the patient enjoyed when younger.
    D. Move the patient to a private room to minimize social contacts after 3 p.m.

12. After 2 months, the patient's agitation increases such that the nursing staff cannot bathe or feed her. Assuming nonpharmacologic approaches are ineffective, which is the best pharmacologic approach to treat her behavioral symptoms?
    A. Increase donepezil to 23 mg daily.
    B. Begin melatonin 6 mg at bedtime.
    C. Add quetiapine 25 mg at 4 p.m. daily.
    D. Add citalopram 10 mg daily.

IV. URINARY INCONTINENCE

A. Epidemiology
    1. Prevalence in community-dwelling older adult women is 38%.
    2. Less common in older adult men: 17%.
    3. Up to 75% of nursing home residents have UI.
    4. Transient incontinence can occur because of DRIP:
        D = Drugs, Delirium
        R = Retention, Restricted Mobility
        I = Impaction, Infection, Inflammation
        P = Polyuria, Prostatitis

B. Physiology
    1. During filling, β_3-adrenergic stimulation relaxes detrusor to increase capacity.
    2. α-Adrenergic stimulation tightens the internal bladder sphincter.
    3. Acetylcholine (M_3 receptors) mediates involuntary and volitional bladder contractions.
    4. Normal bladder emptying occurs with a decrease in urethral resistance and contraction of the bladder muscle.
    5. Aging effects include decreased bladder elasticity and capacity, more frequent voiding, decline in bladder outlet and urethral resistance in women with loss of estrogen, and decrease in flow rate in men with prostatic enlargement.

C. Types of UI

Table 9. Common Types of UI and Drug-Induced Causes

Type of Incontinence	Description	Drug-Induced Causes
Urge or overactive bladder	Loss of a moderate amount of urine with an increased need to void Detrusor instability can be caused by CNS damage from a stroke	Cholinergic agents that stimulate the bladder such as bethanechol and CIs
Stress incontinence	Loss of small amounts of urine with increased abdominal pressure (e.g., sneezing, coughing) Stress UI is more common in postmenopausal women	α-Blockers such as prazosin decrease urethral sphincter tone
Overflow incontinence	Loss of urine because of excessive bladder volume caused by outlet obstruction or an acontractile detrusor PVR is often high (> 300 mL), indicating incomplete emptying	Anticholinergic agents, calcium channel blockers, and opioids decrease detrusor muscle contractions
Functional incontinence	Inability to reach the toilet because of mobility constraints	Sedating drugs that cause confusion Diuretics increase voiding
Mixed incontinence	UI that has more than one cause, usually stress and overactive bladder	

PVR = postvoid residual; UI = urinary incontinence.

D. Nonpharmacologic Interventions
   1. Exercise and weight loss for patients with a body mass index greater than 25–30 kg/m^2
   2. Stress
      a. Pelvic floor exercises (Kegel exercises) are first line for stress.
      b. Biofeedback may be needed to teach pelvic floor exercises.
      c. Stress incontinence usually responds to surgical repair.
      d. Pessaries or bulking agent injections also help stress incontinence.
   3. Urge
      a. Pelvic floor exercises in combination with medication for urge or mixed UI
      b. Bladder training to increase time between voiding in urge incontinence
      c. Peripheral tibial nerve stimulation or sacral neuromodulation techniques are third line after lifestyle and pharmacologic treatments.
   4. Scheduled and timed voiding may be helpful for patients with dementia.
   5. Prostatectomy in men or self-catheterization for severe overflow incontinence

E. Pharmacologic Treatment

Table 10. Recommended Pharmacologic Treatment by Type of Incontinence

Type of Incontinence	Drug Treatment	Comments
Urge or overactive bladder	**Antimuscarinic and anticholinergic agents** Oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, darifenacin	Magnitude of clinical efficacy is modest Differences in adverse reactions exist, but clinical differences in efficacy between these agents have not been shown Longer-acting formulations may be better tolerated
	β_3-Agonist Mirabegron	Appears well tolerated but has not been compared with antimuscarinics
	OnabotulinumtoxinA Intradetrusor or injections	Prevents stimulation of detrusor muscle Pre-procedure antibiotic recommended May cause urinary retention; must be able to perform self-catheterization
Stress	**α-Adrenergic agonists** Pseudoephedrine, phenylephrine	Efficacy evidence is limited
	Topical estrogens Conjugated estrogen vaginal cream or estradiol vaginal insert or ring	Use if other symptoms of estrogen deficiency Vaginal estrogens may improve severity of stress incontinence
	Serotonin/norepinephrine reuptake inhibitor Duloxetine	Not FDA labeled for stress UI; may reduce the severity of incontinence Not significantly different from placebo for symptoms Adverse effects may limit its usefulness
Overflow	**α-Adrenergic antagonists** Alfuzosin, tamsulosin, silodosin, doxazosin, terazosin, prazosin	Adverse effects vary depending on selectivity to receptors in the bladder or prostate (alfuzosin, silodosin, and tamsulosin are more specific and preferred in older adults)
	5-α-reductase inhibitors Finasteride, dutasteride	To slow progression Reduce the size of the prostate and alter PSA values
	Cholinomimetics Bethanechol	Stimulates the detrusor muscle but also systemic cholinomimetic effects
	Phosphodiesterase type 5 inhibitors Tadalafil	5 mg once daily approved for BPH
Functional	No drug treatments	Consider interventions to remove any potential cause, barriers, or obstacles; provide schedules or prompted toileting; assistance may be required to transfer on and off commode
Mixed	Focus on predominating symptoms	Consider treatments for individual components (i.e., stress and urge)

BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen.

Table 11. Comparison of Adverse Effects from Urinary Antimuscarinic Agents[a]

Drug	Dry Mouth	Constipation	Dizziness/Fatigue
Oxybutynin	71.4%	15.1%	16.6%
Oxybutynin ER/XL	up to 72%	up to 15%	≥ 5%
Oxybutynin TDS	4.1%–9.6%	3.3%	N/A
Oxybutynin gel	12.1%	N/A	N/A
Tolterodine IR, ER	23%–35%	6%–7%	2%–5%
Fesoterodine	18.8%–34.6%	4.2%–6%	< 1%
Trospium	20.1%	9.6%	1.9%
Solifenacin	10.9%–27.6%	5.4%–13.4%	1%–2.1%
Darifenacin	20.2%–35.3%	14.8%–21.3%	0.9%–2.1%
Mirabegron	N/A	1.6%	1.2%–1.4%

[a]Sources: Agency for Healthcare Research and Quality (AHRQ). Treatment of Overactive Bladder in Women. AHRQ Publication 09-E017. Rockville, MD: AHRQ, August 2009; data from drug product labeling.

ER/XL = extended release; IR = immediate release; TDS = transdermal delivery system.

Patient Case

13. A 75-year-old woman reports urinary urgency, frequency, and loss of urine when she cannot get to the bathroom in time. She also wears a pad at night that she changes two or three times because of incontinence. Her medical history is significant for MCI (MMSE score 25/30), OA, and hypothyroidism. A urinalysis is negative for leukocyte esterase and nitrites. Physical examination is normal, and her PVR is normal (less than 100 mL). Which therapy would be best to initiate for this patient at this time?

    A. Mirabegron.

    B. Darifenacin.

    C. Pelvic floor exercises and solifenacin.

    D. Pelvic floor exercises and tolterodine immediate release.

V. BENIGN PROSTATIC HYPERPLASIA

A. Epidemiology
   1. BPH usually develops after age 40.
   2. By age 60, 50% of all men have BPH; by age 85, 90% have BPH.

B. Pathophysiology and Clinical Presentation
   1. Type II 5-α-reductase facilitates conversion of testosterone to dihydrotestosterone, resulting in prostate growth.
   2. Lower urinary tract symptoms (LUTS) occur in 25% of men.
      a. Voiding (obstructive) symptoms: Decreased force, hesitancy, dribbling
      b. Storage (irritative) symptoms: Urinary urgency, frequency, nocturia, dysuria
   3. The American Urological Association Symptom Index (AUASI) score can help determine severity and appropriate treatment. The index consists of seven questions evaluating the severity of LUTS on a 0–5 scale. Higher numbers indicate more severe symptoms.

C. Evaluation
   1. Medical history, digital rectal examination, BUN, SCr, and urinalysis
   2. If prostate cancer is suspected, plan treatment with a 5-α-reductase inhibitor, prostate-specific antigen (PSA)
   3. If significant urinary retention is suspected, need to assess PVR. If PVR is greater than 50 mL, patients have an elevated risk of infection.
   4. Assess for medications that may exacerbate BPH symptoms.
      a. α-Adrenergic agonists (decongestants) can stimulate smooth muscle contraction in the prostate and urethra, obstructing urinary flow through the urethra.
      b. Anticholinergic drugs (urinary and GI antispasmodics, antihistamines, tricyclic antidepressants, phenothiazines) can reduce the ability of the bladder detrusor muscle to contract and empty the bladder.
      c. Diuretics can increase urinary frequency and volume.
      d. Testosterone replacement can stimulate prostate growth.
   5. If the AUASI score is 0–7 (mild), use watchful waiting.
   6. Patients with high AUASI scores of 20 and more (severe disease) should be assessed for prostatectomy.
   7. Patients with moderate disease (scores 8–19) are candidates for medical treatment.

D. Pharmacologic Treatment
   1. α-Adrenergic blockers: These relieve LUTS in men with moderate or severe AUASI scores by reducing smooth muscle contractions in the urethra and surrounding tissues.
      a. Nonspecific α-adrenergic blockers such as doxazosin and terazosin also lower blood pressure significantly.
      b. Newer agents are uroselective antagonists of α_1-adrenergic receptors (tamsulosin, silodosin) and selective antagonists of postsynaptic α_1-adrenergic receptors (alfuzosin) in the prostate and bladder. They may have less associated hypotension.
      c. All α-blockers can cause hypotension.
      d. Compared with placebo, α-blockers lower the AUASI score by 4–6 points in patients with LUTS and BPH.
      e. All α-blockers are metabolized through the CYP3A4 pathway and have drug interactions with strong CYP3A4 inhibitors and inducers.
      f. Intraoperative floppy iris syndrome is a concern with α-blockers, especially tamsulosin. Men with LUTS being offered α-blockers should be asked about planned cataract surgery. Men with planned cataract surgery should avoid starting α-blockers until their cataract surgery is completed. If already taking an α-blocker, the patient needs to inform his surgeon so that precautions can be taken.
   2. 5-α-Reductase inhibitors
      a. These agents prevent the conversion of testosterone to dihydrotestosterone, modify the disease course, and may reduce the risk of urinary retention and surgical interventions.
         i. Finasteride competitively inhibits type II 5-α-reductase and lowers prostatic dihydrotestosterone by 80%–90%.
         ii. Dutasteride is a nonselective inhibitor of both type I and II 5-α-reductase. Prostatic dihydrotestosterone production is quickly suppressed with this agent.
         iii. Despite these pharmacologic differences, finasteride and dutasteride did not differ in trials; both reduce prostate size.
      b. 5-α-Reductase inhibitors do not immediately reduce LUTS and should be reserved for use in men with large prostate volume (more than 40 g). At least 6 months of therapy is usually needed for clinical benefit. Prostate size may be reduced by about 25% during this interval.
      c. PSA concentrations are used to monitor for prostate cancer. Because these agents lower PSA concentrations, a baseline PSA test is recommended before initiating α-reductase inhibitors.
      d. Long-term therapy with an α-reductase inhibitor can increase the risk of high-grade tumors of the prostate in healthy men without a history of prostate cancer.

3. Phosphodiesterase type 5 inhibitors
   a. Tadalafil 5 mg once daily is approved for use in BPH.
   b. Mechanism is thought to be caused by phosphodiesterase-induced smooth muscle relaxation in the bladder, urethra, and prostate.
   c. Studied as monotherapy; the FDA does not recommend use in combination with α-blockers because the combination has not been adequately studied for BPH, and there is a risk of lowering the blood pressure. May be used in practice to treat both BPH and erectile dysfunction with a 4-hour separation of doses. If tadalafil is used concomitantly with finasteride to initiate BPH therapy, the recommended therapy duration is 26 weeks or fewer.
4. Combination therapy
   a. May be needed in men with LUTS, a larger prostate size, and an elevated PSA or in men with co-occurring symptoms of erectile dysfunction.
   b. Finasteride and doxazosin are the best studied; dutasteride is FDA label approved for use with tamsulosin in symptomatic men having an enlarged prostate.
   c. Two large clinical trials (Medical Therapy of Prostatic Symptoms [MTOPS] and the Combination of Avodart and Tamsulosin studies [CombAT]) evaluated monotherapy compared with combination therapy and concluded that in men with LUTS and an enlarged prostate, further benefit can be achieved using the two drugs in combination.
   d. Use of an α-blocker together with an anticholinergic agent may be necessary for men with low PVR and irritative symptoms.
5. Supplements
   a. Saw palmetto plant extract (*Serenoa repens*)
      i. Conflicting evidence about the efficacy of saw palmetto in relieving LUTS; 2012 systematic review suggested no benefit over placebo
      ii. Using this agent with 5-α-reductase inhibitors may reduce the efficacy of the reductase inhibitors.
   b. β-Sitosterol, *Pygeum africanum* show some benefit, but short-term studies
6. Surgery is preferred in men with severe symptoms and in those with moderate symptoms who have not adequately responded to medical options.
7. Anticholinergic agents can be appropriate and effective alternatives in men without an elevated PVR when LUTS are predominantly storage (irritative) symptoms.

Table 12. Comparison of Pharmacologic Agents Used for BPH

Medication	Dose Range	Select Adverse Effects	Comments
Terazosin Doxazosin	1–10 mg daily 1–8 mg daily	Orthostatic hypotension	Initiate at low dose; can titrate every 2–7 days Start at bedtime
Alfuzosin ER	10 mg daily	Orthostatic hypotension	No need to titrate Take after a meal
Tamsulosin modified release	0.4–0.8 mg daily	May cause less orthostasis Causes ejaculatory dysfunction	Start at bedtime
Silodosin	8 mg daily 4 mg daily if CrCl 30–50 mL/min/1.73 m^2	Causes ejaculatory dysfunction; appears less sedating	Contraindicated if CrCl < 30 mL/min/1.73 m^2 Take with food

Table 12. Comparison of Pharmacologic Agents Used for BPH *(Cont'd)*

Medication	Dose Range	Select Adverse Effects	Comments
Finasteride Dutasteride Dutasteride/ tamsulosin	5 mg daily 0.5 mg daily 0.5/0.4 mg daily	Decreased libido	Onset of action is usually 6 mo Monitor PSA Pregnancy category X
Tadalafil	5 mg daily	Orthostatic hypotension	Avoid use with α-blockers No data in combination or with long-term use

Patient Case

14. An 85-year-old man with LUTS visits his physician, who determines his AUASI score is 15. His blood pressure is 118/70 mm Hg sitting. A digital rectal examination confirms the diagnosis of BPH, and the physician schedules a further workup including a prostate ultrasound, which shows a prostate volume of 31 g. Which therapy is best at this time?

    A. Terazosin.

    B. Finasteride plus saw palmetto.

    C. Tamsulosin.

    D. Finasteride plus tamsulosin.

VI. OSTEOARTHRITIS

A. Epidemiology
   1. OA is the most prevalent form of arthritis, affecting more than 46 million Americans.
   2. Highly associated with aging: Large weight-bearing joints (e.g., hip and knee) are commonly affected.

B. Etiology and Pathophysiology
   1. Risk factors include age, female sex, obesity, genetics, sports activities, occupation, previous injury, acromegaly, and other chronic illnesses.
   2. Loss of cartilage occurs in the joint as the balance of chondrocyte function shifts from formation to destruction. Secondary inflammation and production of cytokines play a role.
   3. Subchondral bone and the synovium are damaged, and the joint space narrows.
   4. Single injuries or repeated micro-injuries may initiate or accelerate process.
   5. Symptoms of pain result from activation of nociceptive nerve endings in the damaged joint.
   6. Therapy goals: Relieve pain and swelling, maintain or improve joint function, prevent loss of function, and maintain or improve quality of life

C. Nonpharmacologic Treatment
   1. Patient education: Lifestyle, expectations, when to seek care and behavioral, psychosocial, and physical interventions, including self-efficacy and self-management programs to reduce pain and disability
   2. Weight loss decreases the biomechanical load on large weight-bearing joints; even a small amount of weight loss helps decrease pain and disability.
   3. Exercise, including yoga, tai chi
   4. Physical and occupational therapy
   5. Surgery

D. Drug Therapy
   1. NSAIDs are first line; topical agents are preferred, particularly for knee OA, to reduce systemic exposure and adverse effects.
      a. Avoid chronic use, or if necessary, use a cyclooxygenase-2 (COX-2) selective NSAID or add a proton pump inhibitor to reduce the risk of GI bleeding. This recommendation is especially important for older adults.
      b. If one NSAID is not effective, change to others.
      c. Monitor for adverse effects: Rash, abdominal pain, GI bleeding, renal impairment, hypertension, heart failure, and drug-drug interactions
      d. Patients taking aspirin (for cardiac disease) should be educated to take aspirin at least 30 minutes before their first daily NSAID dose in the morning to avoid any interactions or reductions in aspirin efficacy. Naproxen appears to be safest with respect to cardiac risk.
      e. Monitor in chronic users: Complete blood cell count, BUN, SCr, and aspartate aminotransferase at least annually
   2. Topical agents: Topical NSAIDs preferred for knee OA or smaller joints near surface of skin. Limited efficacy for widespread joint pain
      a. Topical capsaicin conditionally recommended for knee OA and conditionally recommended against for hand OA; usually dosed four times daily on a scheduled basis, not as-needed; difficult to administer: Wear gloves, avoid contact with eyes, and do not skip doses. Local irritation occurs in 40% of patients.
      b. Diclofenac 1% gel (or patch is FDA labeled for minor trauma): Four short-term trials showed a 50% reduction in pain in 40% of subjects (number needed to treat = 5); longer-term trials had number needed to treat of 10. Comparative trials with oral administration showed no difference in the proportion of patients who received pain relief.
      c. According to American College of Rheumatology guidelines, topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.
      d. Use of topical rather than oral NSAIDs for patients 75 and older who have hand or knee OA may be preferred to reduce systemic absorption and adverse effects.
   3. Intra-articular glucocorticoid injections
      a. Methylprednisolone or triamcinolone 10- to 40-mg injection depending on size of joint; may be repeated every 3 months
      b. Primary adverse effects are risk of septic arthritis, synovitis
   4. Acetaminophen: In older adults with hepatic impairment or a history of alcohol use disorder using for chronic pain, do not exceed 2–3 g daily.
      a. Alternative to NSAIDs or when NSAID use is contraindicated; very small effect sizes in clinical trials, few of those treated experience important benefit
      b. Monotherapy may be ineffective.
      c. If pharmacologic options are limited because of intolerance of or contraindications to NSAID use, consider for short-term, episodic use.
      d. 1000 mg every 6 hours for up to three times daily or 650 mg every 6 hours. In older adults with hepatic impairment or history of alcohol use disorder using for chronic pain, do not exceed a maximum of 2–3 g daily. 2019 American College of Rheumatology guidelines recommend a maximum dosage of 3 g daily in divided doses.
      e. Ensure that the patient knows to watch for "hidden" acetaminophen in other products.
      f. Monitor for hepatotoxicity in patients with an elevated risk of liver disease (previous liver problems, heavy alcohol consumption) with periodic liver function tests.

5. Dietary supplements: Glucosamine-containing supplements are frequently utilized for relief of osteoarthritis pain
    a. 2019 American College of Rheumatology guidelines strongly recommend against use of glucosamine supplements for relief of knee, hip, and/or hand osteoarthritis
    b. Chondroitin sulfate or combination glucosamine/chondroitin use is recommended against for knee and/or hip osteoarthritis, but conditionally recommended in hand osteoarthritis
    c. Evidence to support treatment is contradictory; many studies are low quality.
    d. The adverse effect profile of glucosamine/chondroitin is similar to that of placebo.
6. Opioids
    a. Patients with persistent, moderate to severe pain from OA who do not respond to more conservative strategies are candidates for opioids.
    b. Tramadol is an alternative when NSAIDs are ineffective or contraindicated; conditionally recommended for patients with knee, hand, and/or hip OA.
    c. Stronger opioids can be more effective but can incur more significant adverse effects; they are conditionally recommended against in patients with knee, hand, and/or hip OA. However, they can be used in certain circumstances when non-opioid alternatives have been exhausted.
    d. Monitor and anticipate opioid adverse effects, and treat accordingly.

Patient Case

15. An 85-year-old man presents with pain from hip OA. He has hypertension, coronary artery disease, and BPH. For his OA, he has been taking acetaminophen 650 mg three times daily. He reports that acetaminophen helps but that the pain persists and limits his ability to walk. Which is the best next step for this patient?

    A. Change acetaminophen to celecoxib.

    B. Add hydrocodone.

    C. Change acetaminophen to ibuprofen.

    D. Add glucosamine.

VII. RHEUMATOID ARTHRITIS

A. Epidemiology
    1. A systemic disease characterized by a bilateral inflammatory arthritis that usually affects the small joints of the hands, wrists, and feet
    2. The prevalence is estimated to be 1%–2%, with women predominating until after age 60, when prevalence becomes equal.
    3. RA can occur at any age but has an increasing prevalence up to age 70.
    4. RA is an autoimmune disease with a strong genetic predisposition.

B. Pathophysiology and Clinical Presentation
    1. Chronic inflammation of the synovium leads to proliferation and development of a pannus.
    2. The pannus invades joint cartilage and eventually causes erosion of the bone and joint destruction.
    3. The cause of the initial inflammatory activation is unknown, but once activated, the immune system produces antibodies and cytokines that accelerate cartilage and joint destruction.
    4. Patients present with joint pain and stiffness, fatigue, and other inflammatory symptoms. Symptoms also include warmth, redness, and swelling of the joints, usually with symmetrical distribution.
    5. Laboratory tests often show a positive rheumatoid factor (RF), elevated sedimentation rate, C-reactive protein, anti–cyclic citrullinated peptide antibodies, and normochromic normocytic anemia.
    6. RA can also affect other organs, causing pulmonary fibrosis, vasculitis, and dry eyes.

C. Treatment
   1. The treatment goal is to control the inflammatory process so that disease remission occurs. This leads to relief of pain, maintenance of function, and improved quality of life. Treatment response can be measured by:
      a. Reduction in the number of affected joints and in joint tenderness and swelling
      b. Improvement in pain
      c. Decreased amount of morning stiffness
      d. Reduction in serologic markers such as RF
      e. Improvement in quality-of-life scales
   2. Nonpharmacologic treatment: Concurrent with pharmacologic treatment
      a. Rest during periods of disease exacerbation
      b. Occupational and physical therapy to support mobility and maintain function
      c. Maintenance of a normal weight (avoid overweight and obesity) to reduce biomechanical stress on joints
      d. Assistive devices if needed
      e. Surgery for tendons or joints
   3. Disease-modifying antirheumatic drugs (DMARDs)
      a. Initiate DMARD within 3 months of diagnosis (methotrexate preferred).
      b. Step-down approach: Start with DMARD (one or more, depending on disease severity) together with anti-inflammatory drug (NSAID, steroid). As pain is controlled, reduce anti-inflammatory agent. As joint damage and inflammation is controlled, reduce DMARD slowly. Do not discontinue all DMARDs, even if patient is in remission.
      c. Nonbiologic DMARDs are first line.
         i. Methotrexate has the most long-term data and better outcomes.
         ii. Hydroxychloroquine has slow onset of action.
         iii. Sulfasalazine is the drug of choice in pregnancy but also has slow onset.
         iv. Leflunomide substitutes, with efficacy comparable with methotrexate.
         v. Some patients with poor prognostic indicators such as functional limitation, extra-articular disease, positive RF, anti–cyclic citrullinated peptide antibodies, or bony erosions on radiography may be candidates for combination DMARD therapy.
      d. Biologic DMARDs are used in combination with methotrexate for severe disease or as alternatives if nonbiologic DMARDs are ineffective or contraindicated.
         i. Tumor necrosis factor (TNF) inhibitors: Etanercept, infliximab, adalimumab, certolizumab, golimumab
         ii. Non-TNF biologics: Abatacept, anakinra, rituximab, tocilizumab, sarilumab
         iii. Biologic kinase inhibitor: Tofacitinib, baricitinib, upadacitinib
      e. Etanercept, infliximab, abatacept, or rituximab is most often used.
   4. NSAIDs, glucocorticosteroids, or both can be used for immediate pain and inflammation relief.
      a. NSAIDs do not affect disease progression in RA; their anti-inflammatory effect occurs within 1–2 weeks of daily dosing, whereas the analgesic effect begins within several hours of administration.
      b. Glucocorticosteroids are not recommended for long-term use because of their many adverse effects and long-term complications. They are often used as bridge therapy to provide anti-inflammatory effects while waiting for the DMARDs to take effect.

D. Comorbid Conditions
   1. Patients with RA are more likely to develop other chronic diseases either from the effects of RA or from the medications used to treat RA.
   2. Cardiovascular disease (myocarditis and heart failure) causes 40% of all deaths in patients with RA. Low-dose aspirin, omega-3 fatty acids, statins, or combination therapy should be considered.
      a. Follow standard guidelines to lower cardiovascular risk factors.
      b. European guidelines recommend multiplying risk score by 1.5 for patients with RA who have disease of 10 years or more, are positive for RF or anti–cyclic citrullinated peptide, or have severe extra-articular disease manifestations (two of the three should be present).
      c. In a patient with congestive heart failure, it is recommended to avoid TNF inhibitors.
   3. Infection risk is elevated, particularly pulmonary infections and sepsis. A history of tuberculosis or hepatitis B calls for extra vigilance.
      a. Tuberculosis screening is required for patients who are considered for therapy with biologic DMARDs.
      b. Immunizations are best given before initiating DMARDs or biologics. A 2-week waiting period is recommended.
      c. Avoid zoster or other live vaccines while the patient is taking DMARDs or biologics.
      d. Patients with hepatitis B or C, if treated with effective antivirals, are treated the same as patients without hepatitis; however, with untreated disease, DMARDs are preferred to TNF inhibitors.

Table 13. Selected DMARDs for RA

Drug	Customary Dose	Comments
Nonbiologic DMARDs		
Methotrexate	7.5–15 mg every week	First-line DMARD for RA; monitor for myelosuppression, liver dysfunction, and pulmonary fibrosis; a teratogen
Leflunomide (Arava)	10–20 mg/day	Similar to methotrexate; an initial loading dose may give therapeutic response within the first month
Hydroxychloroquine (Plaquenil)	200–300 mg twice daily	Must routinely monitor for ocular toxicity; however, this agent has a better adverse effect profile overall
Sulfasalazine	500–1000 mg twice daily	GI adverse effects often limit the use of this agent
Biologic DMARDs		
TNF Inhibitors		
Etanercept (Enbrel)	50 mg SC weekly	Binds to TNF, inactivating this cytokine; generally well tolerated; usually used in those whose methotrexate therapy fails; monitor for infection; check baseline PPD
Infliximab (Remicade, biosimilar version)	3 mg/kg IV at 0, 2, and 6 wk; then every 8 wk thereafter	A mouse/human chimeric antibody to TNF; used in combination with methotrexate to prevent formation of antibodies to this protein; monitor for infection; check baseline PPD
Adalimumab (Humira)	40 mg SC every 2 wk	Human antibody to TNF; less antigenic than other TNF antibodies; monitor for infection; check baseline PPD
Certolizumab pegol (Cimzia)	400 mg SC at 0, 2, and 4 wk; then 200 mg every other week	Monoclonal antibody against TNF; may have best response when used in combination with methotrexate Monitor for infections
Golimumab (Simponi)	50 mg SC every month	Monoclonal antibody against TNF Intended for use in combination with methotrexate Monitor for infections

Table 13. Selected DMARDs for RA *(Cont'd)*

Drug	Customary Dose	Comments
Biologic DMARDs		
Non-TNF Biologics		
Abatacept (Orencia)	Weight-based dose at 0, 2 and 4 wk; then monthly (i.e., 750 mg for those weighing 60–100 kg)	Inhibit interactions between antigens and T cells; may be useful in those who do not respond to TNF inhibitors; monitor for infusion reactions
Anakinra (Kineret)	100 mg SC daily	IL-1 receptor antagonist; avoid combination therapy with TNF agents because of elevated risk of infection
Rituximab (Rituxan)	Two infusions of 1000 mg given 2 wk apart	Chimeric antibody to CD20 protein on B lymphocytes; corticosteroid infusions help reduce infusion reactions; used in combination with methotrexate to improve response
Sarilumab (Kevzara)	200 mg SC once every 2 wk	IL-6 receptor antagonist May use as monotherapy or in combination with nonbiologic DMARDs Should not be used in combination with biologic DMARDs Do not initiate if ANC < 2000/mm^3, platelet count < 150,000/mm^3, or ALT/AST > 1.5 times ULN
Tocilizumab (Actemra)	4 mg/kg IV infusion every 4 wk; can increase to 8 mg/kg on the basis of clinical response	Anti–human IL-6 receptor monoclonal antibody; indicated for patients who have not responded to TNF inhibitors Monitor for infections
Kinase Inhibitor		
Baricitinib (Olumiant)	2 mg daily	Oral Janus kinase inhibitor May be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs Not recommended for use with biologic DMARDs or potent immunosuppressants (azathioprine, cyclosporine) Do not initiate therapy with ANC < 500/mm^3, ANC < 1000/mm^3, or hemoglobin < 8 g/dL
Tofacitinib (Xeljanz)	5 mg twice daily	Oral Janus kinase inhibitor; intended as second-line therapy Can be used as monotherapy or in combination with methotrexate
Upadacitinib (Rinvoq)	15 mg daily	Oral Janus kinase inhibitor May be used as monotherapy or in combination with methotrexate of other nonbiologic DMARDs Not recommended for use with biologic DMARDs or potent immunosuppressants Do not initiate therapy with ANC < 500/mm^3, ANC < 1000/mm^3, or hemoglobin < 8 g/dL

DMARD = disease-modifying antirheumatic drug; IL = interleukin; IV = intravenous(ly); NSAID = nonsteroidal anti-inflammatory drug; PPD = purified protein derivative; RA = rheumatoid arthritis; SC = subcutaneous(ly); TNF = tumor necrosis factor.

4. Malignancy is more common, particularly GI cancers and lymphoproliferative disorders. In addition, melanoma and lung cancer rates were elevated in one cohort study. Use DMARDs over biologics in melanoma; use rituximab over TNF inhibitors in lymphoproliferative disorders.
5. Osteoporosis is more common in patients with RA. Calcium and vitamin D are recommended. In addition, bisphosphonates should be considered for prevention if prednisone 5 mg or more daily is prescribed.

Patient Case

16. A 65-year-old woman received a diagnosis of RA 1 year ago. At that time, her RF titer was 1:64; she presented with joint inflammation in both hands and about 45 minutes of morning stiffness. She began therapy with oral methotrexate and currently receives methotrexate 15 mg weekly, folic acid 2 mg daily, ibuprofen 800 mg three times daily, and omeprazole 20 mg daily. At today's clinic visit, the patient reports the recurrence of her symptoms. Radiographic evaluation of her hand joints reveals progression of joint space narrowing and bone erosion. Which is the next best step for treating this patient's RA?

    A. Administer etanercept.

    B. Change to leflunomide.

    C. Add prednisone bridge therapy.

    D. Change to hydroxychloroquine.

VIII. GOUT

A. Definition: A spectrum of clinical and pathologic features caused by hyperuricemia (serum urate concentrations more than 6.8 mg/dL), resulting in tissue deposition of monosodium urate monohydrate crystals in the extracellular fluid of joints and other sites
    1. Most common rheumatic disease of adults; prevalence estimated at 3.9% of adults (8.3 million) in the United States
    2. Characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain, called acute gouty arthritis, acute gout attacks, or acute gout flares
    3. Also known as monosodium urate crystal deposition disease

B. Diagnosis
    1. Typically presents as acute episodic arthritis
    2. May also present as chronic arthritis of one or more joints, particularly if prolonged hyperuricemia exists
    3. Tophi may be present; detected on physical examination or with imaging
    4. Renal manifestations include uric acid nephrolithiasis and chronic nephropathy.
    5. Features of acute gout attack include:
        a. Severe pain, redness, swelling; maximum severity in 12–24 hours; may continue for a few days to several weeks
        b. Most often affect the lower extremities in a single joint
            i. Most common joint: First metatarsophalangeal joint (podagra) or knee
            ii. May occur in many other joints, including those of upper extremities
            iii. May be polyarticular at first presentation (less than 20% of cases)

6. Ideally, definitive diagnosis should be made by visualization of monosodium urate crystals under polarized compensated light microscopy in fluid aspirated from the affected joint during an acute gout attack.
    a. In the diagnosis of gout, monosodium urate crystals are negatively birefringent (needle shaped or rods).
    b. In pseudogout, crystals are calcium pyrophosphate dihydrate and are weakly positively birefringent (rods or rhomboidal).
    c. Diagnosis by joint aspiration is difficult because patients are in severe pain and often refuse joint aspiration during an acute attack. In this case, a provisional diagnosis can be made according to clinical data.
7. If diagnosis by joint aspiration is not possible, a tentative diagnosis can be made by a combination of presentation or clinical picture and increased uric acid. Use of hyperuricemia as one of the criteria for diagnosing gout may be difficult during an initial acute attack because serum uric acid may be low during flares. The best time to check uric acid is 2 weeks after a flare.

C. Predisposing Factors
1. Dietary: High meat and seafood consumption, fatty foods, dietary overindulgence, high intake of beer and spirits (not wine) in men, sugar-sweetened soft drinks, high-fructose foods
2. Drugs: Xanthine oxidase inhibitors (XOIs) and uricosuric agents (with initial therapy), thiazides and loop diuretics, niacin, calcineurin inhibitors, low-dose aspirin (325 mg/day or less)
3. Medical conditions and other factors: Obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, congestive heart failure, organ transplantation, renal insufficiency, early menopause, trauma, surgery, starvation, dehydration, episodic alcohol consumption

D. Classification
1. Four stages of gout:
    a. Asymptomatic
    b. Acute gouty arthritis
    c. Intercritical gout (intervals between attacks)
    d. Chronic recurrent gout
2. Severities of chronic tophaceous gouty arthropathy (CTGA)
    a. Mild: One joint, stable disease
    b. Moderate: Two to four joints, stable disease
    c. Severe
        i. CTGA of more than four joints *or*
        ii. One or more unstable, complicated, severe articular tophi
    d. Size of joints
        i. Large joints (e.g., knee, ankle, wrist, elbow, hip, shoulder)
        ii. Medium joints (e.g., wrist, ankle, elbow)
        iii. Small joints (e.g., interphalangeal)

E. Treatment Goals
1. The minimum serum urate target is less than 6 mg/dL.
2. A serum urate target of 5 mg/dL or less may be needed to improve gout signs and symptoms. Consider a goal of 5 mg/dL or less if tophi are present.
3. Decrease the frequency of acute gout attacks.

F. Nonpharmacologic Therapy

Table 14. Nonpharmacologic Therapy for Gout[a]

Lifestyle and General Health		
Weight loss if obese Healthy overall diet Exercise Smoking cessation Proper hydration		
Food and Drink to Avoid	**Food and Drink to Limit**	**Food and Drink to Encourage**
Organ meats high in purines (e.g., liver, kidney, sweetbreads)	Serving sizes of: Beef, lamb, pork Seafood with high purine content (e.g., sardines, shellfish)	Low- or nonfat dairy products
High-fructose corn syrup–sweetened sodas, beverages, and foods	Servings of naturally sweet fruit juices Table sugar, sweetened beverages, desserts Table salt	Vegetables
Alcohol overuse (> 2 per day for men, > 1 per day for women) in all patients Any alcohol use during times of frequent gout attacks or advanced gout under poor control	Alcohol (particularly beer but also wine and spirits)	

[a]Note: These approaches are based on a paucity of high-quality evidence on the effects of dietary and lifestyle factors for reducing the risk of recurrent gout attacks.

Adapted from: Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1. Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431-46.

G. Treatment of Acute Gout
   1. Assess severity of gout attack, and select treatment according to severity.
   2. Initiate pharmacologic treatment within 24 hours of onset of an acute gout attack. Colchicine is appropriate only if initiated within 36 hours of attack onset.
   3. Continue established ULT without interruption during acute gout attack (do not discontinue ULT).
   4. Consider oral colchicine, NSAIDs, or glucocorticoids (oral, intra-articular, or intramuscular) as appropriate first-line agents for gout flares.
      a. Choice of colchicine, NSAIDs, or glucocorticoids should be made on the basis of patient factors and preferences.
      b. When colchicine is the chosen agent, low-dose colchicine is recommended over high-dose colchicine, given its similar efficacy and more favorable adverse effect profile. FDA-approved dosing should be followed: 1.2 mg immediately followed by 0.6 mg 1 hour later with ongoing anti-inflammatory therapy until the flare resolves.
      c. For patients who are NPO (nothing by mouth), glucocorticoids (intramuscular, intravenous or intra-articular) are recommended over interleukin-1 (IL-1) inhibitors or ACTH (adrenocorticotropic hormone).
   5. Acute gout attack prophylaxis: Consider initiating concomitant anti-inflammatory prophylactic therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) when initiating ULT.
      a. Selection of specific anti-inflammatory prophylaxis should be based on patient factors.
      b. Continue prophylaxis for 3–6 months, rather than less than 3 months, together with ongoing evaluation and continued prophylaxis as needed for patients who continue to experience flares.

Table 15. Severity, Duration, and Extent of Acute Gout Attacks

Severity[a]	
Mild	≤ 4
Moderate	5 or 6
Severe	≥ 7
Duration Since Onset	
Early	< 12 hr after attack onset
Well established	12–36 hr after attack onset
Late	> 36 hr after attack onset
Extent	
One or a few small joints	
One or two large joints	Large joints: Ankle, knee, wrist, elbow, hip, shoulder
Polyarticular	≥ 4 joints involving > 1 region (regions: forefoot, midfoot, ankle or hindfoot, knee, hip, fingers, wrist, elbow, shoulder) Three separate large joints

[a]Self-reported; based on a 0-to-10 visual analog scale.

Table 16. Medication Dosing for Acute Gout Attack

Drug	**Dose**	**Comments**
Colchicine (Colcrys)	First day: 1.2 mg, then 0.6 mg 1 hr later; day 2 and thereafter: 0.6 mg twice daily until flare resolves CrCl 30–80 mL/min/1.73 m^2: Monitor for adverse effects; dose adjustment not necessary CrCl < 30 mL/min/1.73 m^2: Dose adjustment not necessary but may be considered; do not repeat course of treatment more than every 2 wk Dialysis: 0.6-mg single dose; do not repeat course of treatment more than every 2 wk Severe hepatic impairment: Dose reduction not necessary but may be considered; do not repeat course of treatment more often than every 2 wk	Concomitant use with P-gp inhibitors or strong CYP3A4 inhibitors is contraindicated in renal or hepatic impairment (fatal toxicity has occurred) Colchicine dose should be reduced if renal and hepatic function is normal and if used concomitantly with P-gp inhibitors or moderate to strong CYP3A4 inhibitors
NSAIDs	Naproxen: 750 mg initially, followed by 250 mg every 8 hr Naproxen ER: 1000–1500 mg once daily, followed by 1000 mg once daily Indomethacin: 50 mg three times daily until pain is tolerable; then reduce dose until attack resolves Sulindac: 200 mg twice daily Use anti-inflammatory or analgesic doses of other NSAIDs, same as for treatment of acute pain or inflammation	The only FDA-approved NSAIDs are naproxen, indomethacin, and sulindac; however, other NSAIDs may be as effective Continue full dose until attack completely resolves Can taper dose if comorbidities or renal or hepatic impairment is present
Celecoxib (Celebrex)	800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for 1 wk	Only in certain patients when NSAIDs are contraindicated or not tolerated

Table 16. Medication Dosing for Acute Gout Attack *(Cont'd)*

Drug	Dose	Comments
Glucocorticoids	Prednisone 0.5 mg/kg per day for 5–10 days *or* Prednisone 0.5 mg/kg per day for 2–5 days, then taper for 7–10 days, then discontinue *or* Methylprednisolone dose pack Option for 1 or 2 large joints: Intra-articular corticosteroids Dose based on the size of the joint (e.g., triamcinolone 40 mg for large joint, 30 mg for medium joint, 10 mg for small joint or equivalent) IM triamcinolone 60 mg, followed by oral glucocorticoid (dosing as above)	Intra-articular corticosteroids may be used in combination with OCSs, NSAIDs, or colchicine

OCS = oral corticosteroid.

Table 17. Medication Dosing for Acute Gout Attack Prophylaxis

Drug	Dose	Comments
Colchicine (Colcrys)	0.6 mg once or twice daily (maximum 1.2 mg daily) CrCl 30–80 mL/min/1.73 m^2: Monitor for adverse effects; dose adjustment not necessary CrCl < 30 mL/min/1.73 m^2: Initial dose 0.3 mg/day; use caution and monitor if dose titrated further Dialysis: 0.3 mg twice weekly; monitor for adverse effects Severe hepatic impairment: Dose reduction not necessary but may be considered; do not repeat course of treatment more often than every 2 wk	Concomitant use of colchicine with P-gp inhibitors or strong CYP3A4 inhibitors is contraindicated in renal or hepatic impairment (fatal toxicity has occurred) Colchicine dose should be reduced if renal and hepatic function is normal and if used concomitantly with P-gp inhibitors or moderate to strong CYP3A4 inhibitors
NSAIDs	Lower doses than used for acute attacks (e.g., naproxen 250 mg twice daily, indomethacin 25 mg twice daily)	Consider concomitant proton pump inhibitor or other agent for suppression of PUD, when indicated
Oral glucocorticoids	Prednisone or prednisolone ≤ 10 mg daily	Consider, particularly if colchicine and NSAIDs are both contraindicated, ineffective, or not tolerated

PUD = peptic ulcer disease.

H. Management of Hyperuricemia – Chronic Urate-Lowering Therapy (ULT)
   1. Consider discontinuing nonessential medications that cause hyperuricemia.
   2. Recognize indications for chronic ULT:
      a. One or more subcutaneous tophi on clinical examination or imaging study
      b. Two or more acute gout attacks per year
      c. Radiographic damage as a result of gout

3. ULT can be initiated during an acute gout attack as long as concomitant anti-inflammatory therapy is given.
    a. First line: XOI
        i. Allopurinol or febuxostat; allopurinol preferred first-line agent for all patients, including those with moderate to severe stage 3 chronic kidney disease (CKD) or higher. Start at low dose with dose titration to target over starting at a higher dose.
        ii. Change to alternative XOI (e.g., febuxostat) in patients intolerant of or refractory to first XOI.
    b. Alternative first line: Probenecid
        i. A uricosuric if at least one XOI is contraindicated or not tolerated
        ii. A history of urolithiasis and a CrCl less than 50 mL/minute/1.73 m^2 contraindicate first-line use of probenecid.
        iii. Increased urinary uric acid indicates uric acid overproduction and is a contraindication to use of uricosuric ULT.
    c. Add-on therapy: Lesinurad
        i. Selective uric acid reabsorption inhibitor
        ii. First-in-class
        iii. ONLY as add-on to allopurinol or febuxostat in those who do not achieve serum uric acid concentrations
4. Initiate anti-inflammatory prophylaxis for acute gout concomitantly with or just before ULT in all patients.
    a. There may be an early increase in acute gout attacks during ULT initiation.
        i. May be caused by rapid decrease in urate concentrations, resulting in remodeling of articular urate crystal deposits
        ii. Often leads to nonadherence to ULT, meaning that patient education is critical
    b. Colchicine, NSAIDs, prednisone/prednisolone may be considered
    c. Anti-inflammatory prophylaxis of acute gout should continue for the greater part of 3–6 months, with ongoing evaluation. Anti-inflammatory prophylaxis continued in the presence of any clinical evidence of gout disease activity (tophi, recent acute gout attacks, chronic gouty arthritis)
5. Check serum urate every 2–5 weeks. After goal is achieved, continue monitoring every 6 months. If serum urate goals are not achieved:
    a. Titrate single-agent XOI to maximum appropriate dose.
        i. Allopurinol doses greater than 300 mg/day can be used (even with renal impairment) as long as appropriate patient education and toxicity monitoring are provided (e.g., rash, increased liver function values).
        ii. Substitution of another XOI should be considered if drug intolerance and adverse events occur.
    b. Next, add uricosuric to XOI (probenecid, losartan, or fenofibrate). Probenecid is a first-line uricosuric; losartan and fenofibrate are off-label but are recommended second-line uricosurics.
    c. If the goal serum urate is still not achieved, discontinue other therapies and change to pegloticase only if the gout disease burden is severe *and* the patient's disease is refractory to or the patient is intolerant of other ULT options. Pegloticase is not recommended for first-line therapy in any case.
6. Allopurinol hypersensitivity syndrome (AHS) is possible.
    a. Risk of severe morbidity and hospitalization
    b. Mortality rate of 20%–25% in AHS
    c. Manifestations: Stevens-Johnson syndrome, toxic epidermal necrolysis, clinical constellation of symptoms (eosinophilia, rash, vasculitis, major end-organ disease)
    d. Highest risk during the first few months of therapy
    e. Risk factors: Concomitant thiazide diuretics, renal impairment, Han Chinese or Thai descent (irrespective of renal function), Korean descent with stage 3 CKD or worse. Consider testing for *HLA-B*5801* in these ethnic groups (presence indicates higher risk of AHS).

Table 18. Chronic ULT

Drug	Dose	Comments
Allopurinol (Zyloprim)[a]	Starting dose: 100 mg daily (50 mg daily in stage 4 CKD) Gradually titrate dose every 2–5 wk to appropriate maximum dose (800 mg daily with normal renal function) or until goal urate concentration reached Maintenance dose can be > 300 mg daily, even in CKD, as long as patient is educated and regular monitoring occurs for hypersensitivity, rash, pruritus, elevated hepatic enzymes, and eosinophilia	XOI Low starting dose reduces early gout flares and risk of hypersensitivity syndrome Consider keeping dose lower in CKD and not increasing to maximum dose; data with dosing > 300 mg/day in CKD are limited Dose reduction algorithms in CKD have been developed but are not evidence based; the ACR guidelines do not recommend following them
Febuxostat (Uloric)[a]	Starting dose: 40 mg once daily May increase dose to 80 mg once daily if goal serum urate not reached CrCl < 30 mL/min/1.73 m^2: Use caution; insufficient data	XOI More expensive than allopurinol; no generic available FDA black box warning: Increased risk of death compared with allopurinol
Lesinurad (Zurampic)	200 mg once daily Do not use if CrCl < 45 mL/min/1.73 m^2	Selective urate reabsorption inhibitor Not for use as monotherapy Not for use if asymptomatic hyperuricemia Potential increase in cardiovascular events
Lesinurad/ allopurinol (Duzallo)	200 mg/200 mg or 200 mg/300 mg once daily Do not use if CrCl < 45 mL/min/1.73 m^2	Combination urate reabsorption inhibitor and XOI Indicated when serum uric acid concentrations not achieved with allopurinol alone Continue the same allopurinol dose (200 mg or 300 mg) when initiating the combination product
Probenecid (generic only)[a]	Starting dose: 250 mg twice daily May increase weekly in 500-mg/day increments to maximum dose of 1 g twice daily, if needed Avoid if CrCl < 30 mL/min/1.73 m^2	Uricosuric; first line According to the guidelines, not recommended for first-line or alternative first-line treatment if CrCl < 50 mL/min/1.73 m^2 or history of urolithiasis Do baseline and periodic urine uric acid; elevated urine uric acid concentration (uric acid overproduction) is contraindication When initiating, increase fluid intake and consider urine alkalinization (e.g., potassium citrate)
Losartan	Dose according to other indications and as tolerated	Uricosuric; second line Off-label use
Fenofibrate	Dose according to other indications and as tolerated	Uricosuric; second line Off-label use
Pegloticase (Krystexxa)[a]	8 mg IV every 2 wk No dose adjustment for CKD	Use only if severe gout disease burden *and* refractory to or intolerant of other ULT options All other antihyperuricemic agents must be discontinued before initiation of pegloticase; do not administer concomitantly Premedicate with antihistamines and corticosteroids

[a]Always initiate concomitant prophylactic therapy.ACR = American College of Rheumatology; CKD = chronic kidney disease; ER = extended release; IM = intramuscular(ly); NSAID = nonsteroidal anti-inflammatory drug; P-gp = P-glycoprotein; PUD = peptic ulcer disease; ULT = urate-lowering therapy; XOI = xanthine oxidase inhibitor.

Patient Cases

Questions 17–19 pertain to the following case.

A 60-year-old man (weight 80 kg) presents with his third gout attack of the past year. His last attack, for which he took colchicine with good response, was 10 days ago. He is experiencing pain in his left knee and in the third and fourth proximal interphalangeal joints on his left hand. The pain started about 10 hours ago. The patient rates his pain as 6/10. He has chronic obstructive pulmonary disease and dyslipidemia, and his renal function is normal. His uric acid concentration 1 month ago was 10 mg/dL. He has no tophi. His only medications are inhaled tiotropium, albuterol, and simvastatin.

17. Which is most appropriate for treatment of this acute gout attack?
    A. Naproxen 750 mg, then 250 mg every 8 hours.
    B. Colchicine 1.2 mg, then 0.6 mg in 1 hour, then 0.6 mg every 12 hours.
    C. Intra-articular triamcinolone injection of all affected joints.
    D. Prednisone 40 mg daily plus naproxen 750 mg, then 250 mg every 8 hours.

18. Assuming this patient will be receiving acute anti-inflammatory therapy, which decision is most appropriate regarding ULT in this patient?
    A. Probenecid should be initiated, but treatment should be delayed until after the acute attack has resolved.
    B. Probenecid should be initiated and can be initiated during the acute attack.
    C. Oral allopurinol should be initiated, but treatment should be delayed until after the acute attack has resolved.
    D. Oral allopurinol should be initiated and can be initiated during the acute attack.

19. Which regimen for anti-inflammatory prophylaxis with ULT is most appropriate for this patient once the acute attack has resolved?
    A. Colchicine 0.6 mg daily.
    B. Prednisone 10 mg daily.
    C. Colchicine 0.6 mg daily plus naproxen 250 mg twice daily.
    D. Pegloticase 8 mg intravenously every 2 weeks.

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REFERENCES

Principles to Promote Optimal Medication Use in Older Adults

1. AGS Expert Panel on the Care of Older Adults with Multimorbidity. Patient-centered care for older adults with multiple chronic conditions: a stepwise approach from the American Geriatrics Society. J Am Geriatr Soc 2012;60:1957-68.
2. American Geriatrics Society (AGS). American Geriatrics Society 2019 Updated AGS Beer Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2019;67:674-94.
3. American Geriatrics Society (AGS). Ten Things Physicians and Patients Should Question. Released February 21, 2013 (1–5) and February 27, 2014 (6–10) and April 23, 2015 (2, 3, 6, 7, 8, 10). Available at https://www.choosingwisely.org/societies/american-geriatrics-society/ Accessed September 20, 2019.
4. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Creatinine Based Equations. Available at http://ckdepi.org/equations/creatinine-based-equations/. Accessed September 20, 2019.
5. Dowling TC, Wang ES, Ferrucci L, et al. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. Pharmacotherapy 2013;33:912-21.
6. Elliott DP. Pharmacokinetics and pharmacodynamics in the elderly. In: Schumock G, Brundage D, Chapman M, et al., eds. Pharmacotherapy Self-Assessment Program, 5th ed. Lenexa, KS: American College of Clinical Pharmacy, 2004:115-30.
7. Hajjar ER, Gray SL, Slattum PW, et al. Chapter e7. Geriatrics. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. Available at https://accesspharmacy.mhmedical.com/Content.aspx?bookid=1861&sectionid=146077984. Accessed September 20, 2019.
8. Handler SM, Wright RM, Ruby CM, et al. Epidemiology of medication-related adverse events in nursing homes. Am J Geriatr Pharmacother 2006;4:264-72.
9. Higashi T, Shekelle PG, Solomon DH, et al. The quality of pharmacologic care for vulnerable older patients. Ann Intern Med 2004;140:714-20.
10. Hutchison LC, O'Brien CE. Changes in pharmacokinetics and pharmacodynamics in the elderly patient. J Pharm Pract 2007;20:4-12.
11. Inouye SK, Studenski S, Tinetti ME, et al. Geriatric syndromes: clinical, research and policy implications of a core geriatric concept. J Am Geriatr Soc 2007;55:780-91.
12. Labella AM, Merel SE, Phelan EA. Ten ways to improve the care of elderly patients in the hospital. J Hosp Med 2011;6:351-7.
13. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. Arch Intern Med 2007;167:1752-9.
14. National Kidney Foundation (NKF). Glomerular Filtration Rate. Available at https://www.kidney.org/sites/default/files/docs/12-10-4004_abe_faqs_aboutgfrrev1b_singleb.pdf. Accessed June 22, 2016.
15. Onder G, van der Cammen TJM, Petrovic M, et al. Strategies to reduce the risk of iatrogenesis in complex older adults. Age Ageing 2013;42:284-91.
16. Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. Clin Pharmacol Ther 2007;82:87-96.

Dementia

1. Alzheimer's Association. Health Care Professionals and Alzheimer's. 2017. Available at www.alz.org/health-care-professionals/health-care-clinical-medical-resources.asp. Accessed December 12, 2017.
2. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD005593.
3. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734-46.
4. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA Cooperative randomized trial. JAMA 2014;311:33-44.

5. Gill SS, Anderson GM, Fischer HD, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors. Arch Intern Med 2009;169:867-73.
6. Hilas O, Ezzo DC. Dementias and related neuropsychiatric issues. In: Richardson M, Chant C, Cheng JWM, et al., eds. Pharmacotherapy Self-Assessment Program, 7th ed. Neurology and psychiatry. Lenexa, KS: American College of Clinical Pharmacy, 2012:91-110.
7. Howard R, Lindesay J, Ritchie C, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012;366:893-903.
8. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911-22.
9. Linnebur SA. Geriatric assessment. In: Hutchison LC, Sleeper RB, eds. Fundamentals of Geriatric Pharmacotherapy. Bethesda, MD: American Society of Health-System Pharmacists, 2010:71-90.
10. National Institute on Aging (NIA). Alzheimer's Diagnostic Guidelines. Available at www.nia.nih.gov/research/dn/alzheimers-diagnostic-guidelines. Accessed June 22, 2016.
11. Peron EP, Slattum PW, Powers KE, et al. Chapter 54. Alzheimer's disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. Available at http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146062470.
12. Qaseam A, Snow V, Cross JT, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008;148:370-8.
13. Rabins PV, Blacker D, Rovner BW, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry 2007;164(12 suppl):5-56.
14. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148:379-97.
15. Rubin CD. The primary care of Alzheimer disease. Am J Med Sci 2006;332:314-33.

Behavioral Symptoms of Dementia

1. Agency for Healthcare Research and Quality (AHRQ). Off-Label Use of Atypical Antipsychotics: An Update. September 27, 2011. Available at https://www.effectivehealthcare.ahrq.gov/topics/atypical-antipsychotics-off-label-update/. Accessed December 12, 2017.
2. Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomized placebo-controlled trial. Lancet Neurol 2009;8:151-7.
3. Ballard C, Sharp S, Corbett A. Dextromethorphan and quinidine for treating agitation in patients with Alzheimer disease dementia. JAMA 2015;314:1233-5.
4. Ballard CG, Waite J, Birks J. Atypical antipsychotics for aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD003476.
5. Banerjee S, Hellier J, Romeo R, et al. Study of the use of antidepressant for depression in dementia: the HTA-SADD trial—a multicentre, randomized, double-blind, placebo-controlled trial of the clinical effectiveness and cost effectiveness of sertraline and mirtazapine. Health Technol Assess 2013;17:1-166.
6. Grimmer T, Kurz A. Effects of cholinesterase inhibitors on behavioural disturbances in Alzheimer's disease: a systematic review. Drugs Aging 2006;23:957-67.
7. Howard RJ, Juszczak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. N Engl J Med 2007;357:1382-92.
8. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults. JAMA 2011;306:1359-69.
9. Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia. Number needed to harm. JAMA Psychiatry 2015;72:438-45.
10. Sadowsky CH, Galvin JE. Guidelines for the management of cognitive and behavioral problems in dementia. JABFM 2012;25:350-66.

11. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia. Meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934-43.
12. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525-38.
13. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia. A review of the evidence. JAMA 2005;293:596-8.
14. Sutor B, Rummans TA, Smith GE. Assessment and management of behavioral disturbances in nursing home patients with dementia. Mayo Clin Proc 2001;76:540-50.
15. Yury CA, Fisher JE. Meta-analysis of the effectiveness of atypical antipsychotics for the treatment of behavioural problems in persons with dementia. Psychother Psychosom 2007;76:213-8.

Urinary Incontinence and Benign Prostatic Hypertrophy

1. American Urological Association (AUA). Clinical Guidelines. Management of Benign Prostatic Hyperplasia. 2010 (reviewed and validity confirmed 2014). Available at www.auanet.org/guidelines/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014). Accessed December 12, 2017.
2. Edwards JL. Diagnosis and management of benign prostatic hyperplasia. Am Fam Physician 2008;77:1403-10.
3. Filson CP, Hollingsworth JM, Clemens JQ, et al. The efficacy and safety of combined therapy with α-blockers and anticholinergics for men with benign prostatic hyperplasia: a meta-analysis. J Urol 2013;190:2153-65.
4. Gormley EA, Lightner DJ, Burglio KL, et al. Diagnosis and Treatment of Overactive Bladder (non-neurogenic) in Adults: AUA/SUFU Guideline. American Urological Association, May 2012, updated 2014.
5. Huang A. Nonsurgical treatments for urinary incontinence in women. Summary of primary findings and conclusions. JAMA 2013;173:1463-4.
6. Kaplan SA, Roehrborn CG, McConnell JD, et al. Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the full range of baseline prostate sizes in men enrolled in the MTOPS trial. J Urol 2008;180:1030-3.
7. Porst H, Oelke M, Goldfischer ER, et al. Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. Urology 2013;82:667-73.
8. Rees J, Bultitude M, Challacombe B. The management of lower urinary tract symptoms in men. BMJ 2014;348:g3861.
9. Roehrborn CG, Siami P, Barkin J, et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. J Urol 2008;179:616-21.
10. Rogers R. Urinary stress incontinence in women. N Engl J Med 2008;358:1029-36.
11. Tacklind J, MacDonald R, Rutks I, et al. *Serenoa repens* for benign prostatic hyperplasia. Cochrane Database Syst Rev 2012;12:CD001423.
12. Wood LN, Anger JT. Urinary incontinence in women. BMJ 2014;349:g4531.
13. Yamaguchi O, Nishizawa O, Takeda M, et al. Clinical guidelines for overactive bladder. Int J Urol 2009;16:126-42.

Osteoarthritis, Rheumatoid Arthritis, and Gout

1. American Geriatrics Society (AGS). Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57:1331-46.
2. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795-808.
3. Eriksson J, Neovius M, Bratt J, et al. Biological vs conventional combination treatment and work loss in early rheumatoid arthritis. A randomized trial. JAMA Intern Med 2013;173:1407-14.

4. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res 2020;72:744-60.
5. Fosbol E, Folke F, Jacobsen S, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes 2010;3:395-405.
6. Hochberg MC, Martel-Pelletier J, Monfort J, et al. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicenter, randomized, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis 2016;75:37-44.
7. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2020 Jan 6. [Epub ahead of print]. Available at https://www.rheumatology.org/Portals/0/Files/Osteoarthritis-Guideline-Early-View-2019.pdf. Accessed January 24
8. O'Dell JR, Curtis JR, Mikuls TR, et al. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. Arthritis Rheum 2013;65:1985.
9. Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-31.
10. Qaseem A, McLean RM, et al.; Clinical Guidelines Committee of the American College of Physicians. Diagnosis of acute gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:52-7.
11. Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. Cochrane Database Syst Rev 2015;1:CD005614.
12. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res 2015;68:1-25.
13. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;72:492-509.
14. Stoffer MA, Schoels MM, Smole JS, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016;75:16-22.
15. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005;2:CD002946.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

Renal elimination is usually the most significantly changed pharmacokinetic value in older adults. This patient's advanced age and diseases will add to her loss of renal function. Using the Cockcroft-Gault equation, this patient's estimated CrCl is 24 mL/minute/1.73 m^2. Creatinine clearance = [(140 − 85) × 65]/[(72 × 1.8)] × 0.85. At this level of function, glyburide elimination would be prolonged, and metformin use is contraindicated (Answer D is correct). The aspirin is low dose, and melatonin is safe even at very high doses (Answer A is incorrect). Although lisinopril is renally eliminated, dosing is based on response, and meclizine has mostly hepatic metabolism with no dosage adjustment in renal insufficiency (Answer B is incorrect). Answer C is incorrect because lisinopril, unlike glyburide, is not considered potentially inappropriate in older adults.

2. Answer: B

Common pharmacodynamic changes associated with aging include impaired homeostasis for electrolytes with angiotensin-converting enzyme inhibitors such as lisinopril and increased sensitivity to anticholinergic adverse effects from drugs such as meclizine (Answer B is correct). Lisinopril, metformin, and glyburide have primarily pharmacokinetic problems because of renal excretion changes when used in older adults (Answers C and D are incorrect). Melatonin is extremely safe without pharmacodynamic or pharmacokinetic issues in older adults, and the aspirin is low dose, so issues with GI bleeding are less than with higher doses (Answer A is incorrect).

3. Answer: A

Glipizide and simvastatin are not listed in the 2019 AGS Beers Criteria tables (Answer B is incorrect). In addition to glipizide not being listed, the patient's CrCl is greater than 30 mL/minute/1.73 m^2, and nitrofurantoin is not for long-term suppression of bacteria (Answer C is incorrect). Histamine-2 receptor antagonists are no longer recommended to avoid in patients with dementia or cognitive impairment because of weak evidence of adverse cognitive effects, and neither metoprolol nor clopidogrel is listed (Answer D is incorrect). However, paroxetine should be used with caution in patients with hyponatremia; donepezil as a CI should be avoided in patients with syncope because it can cause bradycardia; and tolterodine has strong anticholinergic properties and should be avoided in patients with dementia (Answer A is correct).

4. Answer: B

Fluticasone/salmeterol meets the 10 criteria for the Medication Appropriateness Index (Answer A is incorrect). Ranitidine has no listed indication in this patient, clopidogrel has exceeded the recommended therapy duration for her stent, and metoprolol has a significant drug-drug interaction with donepezil, given her bradycardia (Answer B is correct). Aspirin is indicated because preventive therapy meets the other nine criteria of the Medication Appropriateness Index (Answer C is incorrect). Nitrofurantoin has been initiated for a presumptive urinary tract infection, given her history of frequent urinary tract infections, and simvastatin is appropriate for her disease and condition (Answer D is incorrect).

5. Answer: C

Because the patient's A1C is less than 7.5%, glipizide should be reevaluated; donepezil use in dementia requires periodic reassessment of risk-benefit; and asymptomatic bacteriuria should not be treated with antimicrobials; these medications should be evaluated for continued need and possible discontinuation, according to the Choosing Wisely criteria (Answer C is correct). Paroxetine, ranitidine, and tolterodine are not addressed by these criteria (Answer A is incorrect). Similarly, metoprolol, clopidogrel, and tolterodine are not addressed by these criteria (Answers B and D are incorrect).

6. Answer: D

This patient had a geriatric syndrome (a fall) and hazards of hospitalization (decline in organ systems and function) that occur with many older adult patients. At this time, she has several risk factors for another fall, including a history of falls, diseases such as diabetes and hypertension, dizziness, and use of several drugs. An assessment of gait and balance would help determine the severity of her risk (Answer D is correct). Although the IADL assessment is overall good and functional, it does not focus on the risks associated with increased falls (Answer A is incorrect). Evaluating the presence or severity of depression or of pressure sores would not

be a functional assessment, though it would affect functional abilities (Answers B and C are incorrect).

7. Answer: C
Efforts to maintain bone and muscle strength are more important for this patient than is primary prevention of cardiovascular disease with atorvastatin or lisinopril. Most older adults do not consume a diet rich in vitamin D; moreover, most older adults have less sun exposure and are more likely to be deficient in vitamin D, which is a risk factor for falls and reduced muscle strength. Furthermore, naproxen is not a good alternative for the patient because of increased risk of GI bleeding and worsening renal function (Answer C is correct). Although simvastatin and lisinopril can prevent complications caused by cardiovascular disease after extended use, they do not improve functional abilities in the short term (Answers A and B are incorrect). Pain management is important for functional status, but use of opioids compared with non-opioids has not been associated with differences in functional status (Answer D is incorrect).

8. Answer: B
This patient has a positive screen for mild dementia. However, when evaluating her cognitive loss, it is important to limit the use of any drug that could contribute to confusion, such as those identified on the AGS Beers Criteria, before treating for an unconfirmed condition (Answer A is incorrect). Anticholinergics such as tolterodine can cause confusion, so it would be best to discontinue this agent and reassess cognition before treating for AD (Answer B is correct). In addition, before initiating vitamin B_{12} injections, the patient should have laboratory evidence of deficiency (Answer C is incorrect). Without a serum sodium concentration, there is no reason to expect that hydrochlorothiazide would cause her cognitive decline, so changing to lisinopril is not indicated at this time (Answer D is incorrect).

9. Answer: B
Rivastigmine is a potent inhibitor of acetyl and butyryl cholinesterase, leading to significant cholinergic adverse effects such as nausea, vomiting, and diarrhea. However, use of the transdermal delivery system generates even plasma concentrations and lessens the incidence of cholinergic adverse effects. Because the maintenance dose has been achieved with rivastigmine 12 mg, this patient can change to the patch that delivers 9.5 mg/day (Answer B is correct). Antacids will not substantially alleviate the GI effects of CIs, and prochlorperazine is anticholinergic (Answers A and D are incorrect). Because rivastigmine appears to work, it is better to continue its use, if possible, than to change to memantine (Answer C is incorrect).

10. Answer: B
Over 3 years, this patient's MMSE score has decreased only 4 points, which suggests a treatment response to donepezil. Furthermore, the patient can still live at home with her husband, and she has maintained some function in her basic ADLs. However, she has not responded to a higher donepezil dose, and there is no evidence that retrying it later is useful (Answer A is incorrect). Changing from one CI to another is not effective (Answer D is incorrect). Because she has benefited from donepezil use, she should not abruptly discontinue it. Some clinical trials with memantine show an additional treatment response when memantine is added to donepezil therapy. When the benefits, risks, and costs have been openly discussed and the family prefers to consent to therapy, a time-based trial is reasonable. Memantine should be initiated at 5 mg daily (Answer B is correct). Donepezil can be evaluated for tapering after memantine titration. Vitamin E has shown no effect in most large prospective trials of AD and is not first choice to provide benefit (Answer C is incorrect).

11. Answer: C
Patients in the late stages of dementia (as evidenced by an MMSE score of 5/30) with behavior issues would benefit most from nonpharmacologic treatment such as music therapy (Answer C is correct). Social isolation would likely increase symptomatology, and haloperidol is not recommended until nonpharmacologic treatments have failed or patients have become a harm to themselves or others. In addition, the haloperidol dose is excessive, with risk outweighing benefit (Answers B and D are incorrect). Although pain control may be useful, ibuprofen is not the first drug of choice and has more risk of harm than benefit in a frail older adult patient (Answer A is incorrect).

12. Answer: C
Increasing the dose of a CI has not been shown to reduce agitation with dementia (Answer A is incorrect). The patient has become a harm to self (because of refusing

care), so a course of quetiapine is appropriate, assuming other nonpharmacologic treatments have been tried unsuccessfully (Answer C is correct). Citalopram has small studies showing evidence of effectiveness in the literature, but its role in therapy for agitation is unclear (Answer D is incorrect). No sleep disturbance is noted, so melatonin is unlikely to help (Answer B is incorrect).

13. Answer: C

This patient has symptoms of urge incontinence. Pelvic floor exercises in conjunction with drug therapy should be offered for initial therapy (Answer C is correct). Darifenacin alone is not the best treatment (Answer B is incorrect). Some evidence indicates that solifenacin, a selective muscarinic blocker, does not worsen cognition, and solifenacin would be preferred to tolterodine in this patient with MCI (Answer D is incorrect). Mirabegron, a newer agent with less evidence for its exact role in therapy, should not be offered without pelvic floor exercises (Answer A is incorrect).

14. Answer: C

Pharmacologic therapy targeted at reducing urethral sphincter pressure has proved effective in reducing BPH symptoms. Tamsulosin is an α-adrenergic blocker with more specific activity for the genitourinary system. Given that the patient already has low normal blood pressure, tamsulosin would be preferred to terazosin (Answer C is correct; Answer A is incorrect). Orthostatic hypotension can still occur with all α-adrenergic blockers, so patients should be monitored when therapy is initiated. Finasteride, a 5-α-reductase inhibitor, and combination therapy with 5-α-reductase inhibitors are recommended when there is evidence of large prostate (Answer D is incorrect). Saw palmetto is not recommended in combination with 5-α-reductase inhibitors because it may reduce their efficacy (Answer B is incorrect).

15. Answer: B

The AGS recommends opioids for OA when older patients do not respond to initial therapy with acetaminophen (Answer B is correct). The NSAIDs and COX-2 inhibitors are seldom considered when a thorough assessment of the patient reveals that the risk of treatment (GI bleeding and worsening renal function) does not outweigh the potential benefit (Answers A and C are incorrect). Glucosamine can be added to this patient's medication regimen; however, even if effective, it will not provide immediate pain relief (Answer D is incorrect).

16. Answer: A

This woman has indicators of a poor prognosis with RA (positive RF, many symptoms) and has not responded to methotrexate therapy. Although the next treatment step is not entirely clear, her best choices are between double- or triple-combination DMARD therapy and a biologic agent. Leflunomide or hydroxychloroquine would not be recommended as monotherapy for someone who has not responded to methotrexate (Answers B and D are incorrect). Etanercept has a response in 60%–75% of patients whose therapy with methotrexate has failed (Answer A is correct). Glucocorticosteroids are used as adjunctive therapy for the first several months of treatment with a disease-modifying agent and would be inadequate at this time (Answer C is incorrect).

17. Answer: A

The NSAIDs (in anti-inflammatory or acute pain doses), colchicine, and corticosteroids are all appropriate first-line therapy for acute gout. Answer A is correct because the listed regimen of naproxen is appropriate first-line therapy for acute gout. Answer B is incorrect; colchicine would not be recommended for this patient because he took acute colchicine doses in the past 2 weeks. Intra-articular corticosteroids are recommended only if only one or two large joints are affected; therefore, Answer C is incorrect because the patient has pain in several small joints. This patient is having an acute gout attack of moderate severity. Answer D is incorrect because combination therapy is recommended for initial therapy only if the patient has a severe attack. Oral prednisone alone would also be appropriate; however, this was not a choice.

18. Answer: D

Urate-lowering therapy is indicated in this patient because he has had two or more attacks in the past year. Allopurinol and febuxostat (XOIs) are first-line ULTs. Answers A and B are incorrect because probenecid is an alternative first-line ULT only if XOIs are contraindicated or not tolerated. Urate-lowering therapy can be initiated during an acute gouty attack, according to the ACR guidelines, as long as anti-inflammatory prophylaxis is instituted, which makes Answer C incorrect. Answer D is correct because it incorporates appropriate ULT in the form of allopurinol and can be initiated

during the acute attack as long as the patient is also receiving anti-inflammatory prophylaxis.

19. Answer: A

Oral low-dose colchicine is the first-line option for anti-inflammatory prophylaxis with ULT, making Answer A correct. Answer B is incorrect because oral glucocorticoids are associated with significant risks in long-term therapy and should not be used for anti-inflammatory prophylaxis unless both colchicine and NSAIDs are contraindicated, not tolerated, or ineffective. Combination therapy is not recommended for anti-inflammatory prophylaxis, making Answer C incorrect. Answer D is incorrect because pegloticase is used for ULT, not anti-inflammatory prophylaxis.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A
Diazepam is a long-acting benzodiazepine that can accumulate in older patients, resulting in excessive lethargy, sedation, and unsteady gait, and the patient admits taking it every night during the past week (Answer A is correct). A worsening of the patient's depression is evident with the recent bereavement; however, that would not explain the unsteady gait (Answer D is incorrect). Lisinopril is not likely to cause this problem with his blood pressure at target, and atorvastatin is not a common cause of lethargy and confusion (Answers B and C are incorrect).

2. Answer: C
In older patients, the volume of distribution of lipid-soluble drugs such as diazepam is increased, not decreased (Answer D is incorrect). In addition, changes in metabolism through phase I (oxidation) are diminished (Answer C is correct). Diazepam tends to accumulate with reduced capacity for elimination, resulting in excessive sedation and an increased risk of falls in older patients. Oral absorption is not significantly altered in older adults for chronic medications (Answer A is incorrect). Decreased renal excretion is likely but is not a significant contributor in this patient, given the drugs on his medication list (Answer B is incorrect).

3. Answer: B
The patient has no symptoms of hypotension; therefore, no changes in her metoprolol therapy are warranted (Answer C is incorrect). Insufficient information is provided to determine the need to add memantine at this time (Answer A is incorrect). Adding vitamin D to this resident's regimen, given her deficient serum concentrations, may help reduce falls (Answer B is correct). Adding calcium carbonate might help reduce fractures but would not reduce fall risk (Answer D is incorrect).

4. Answer: B
An initial trial of acetaminophen at doses less than 3 g/day is reasonable for frail patients with OA pain (Answer B is correct). Ibuprofen and tramadol would be alternatives when more conservative medications have failed a trial of 1–2 weeks (Answers A and C are incorrect). As-needed hydrocodone/acetaminophen should be used cautiously in older patients who have significant osteoarthritic pain and cannot tolerate other drugs (Answer D is incorrect).

5. Answer: D
All CIs have similar efficacy. The rivastigmine transdermal patch is better tolerated than the oral dosage formulation. Donepezil tends to be better tolerated than the other oral CIs. Doses of cholinesterase medications should be titrated slowly to prevent GI upset. The initial donepezil dose is 5 mg daily at bedtime, and for galantamine ER, the dose is 8 mg once daily (Answers A and B are incorrect). The rivastigmine patch 4.6 mg is the appropriate initial starting dose (Answer D is correct). Memantine has no beneficial effect in maintaining cognitive function, as measured by MMSE scores (Answer C is incorrect).

6. Answer: A
This patient's current fasting blood glucose of 65 mg/dL and A1C of 5.6% should prompt the pharmacist to request glipizide discontinuation (Answer A is correct). According to the American Diabetes Association's Standards of Medical Care in Diabetes guidelines, older adults with several chronic illnesses, cognitive impairment, or functional dependence should have less stringent glycemic goals, such as A1C less than 8.0%–8.5%. The goals of therapy are to prevent hypoglycemia in older patients at greatest risk of this adverse drug reaction. There is no rationale for reducing the carvedilol dose, and given her normal basic metabolic panel and blood pressure, reducing potassium chloride or discontinuing lisinopril is not indicated at this time (Answers B–D are incorrect).

7. Answer: D
No evidence at this time supports increasing the donepezil dose to 23 mg to manage behavioral symptoms of dementia (Answer C is incorrect). The off-label use of atypical antipsychotic medications in patients with behavioral symptoms of dementia should be reserved for patients who pose a danger to themselves or others or experience hallucinations or delusions that are stressful to them (Answers A and B are incorrect). Adding acetaminophen to treat possible pain that could be causing the patient's behavior should be tried before more aggressive strategies (Answer D is correct).

8. Answer: A

Any new symptom of UI in an older adult should be thoroughly evaluated to determine whether there is a reversible cause. Infection, or the "I" in the mnemonic DRIP, may be the cause of the new symptoms in this patient. Urinalysis would be the most appropriate intervention for this reversible cause of incontinence (Answer A is correct). Tolterodine is used in urge incontinence that does not respond to an adequate pelvic floor muscle trial (Answer C is incorrect). Duloxetine has been used off-label for stress incontinence (Answer D is incorrect). Pelvic floor muscle exercises or Kegel exercises should be first-line therapy for stress, urge, or mixed incontinence in women (Answer B is incorrect).

9. Answer: C

In this patient with comorbid conditions of hypertension and BPH, the choice of α-blockers is based on the adverse effect profiles. This patient has an elevated PVR volume, so changing tamsulosin to terazosin might reduce both blood pressure and urinary retention; merely changing to another selective α-blocker might not provide adequate relief of both conditions. (Answer C is correct; Answer A is incorrect). Increasing the atenolol dose would address only the increased blood pressure, without affecting the current problem of acute urinary retention (Answer B is incorrect). The patient is receiving moderate doses of controlled-release opioid, so reducing the hydromorphone dose for breakthrough pain is unlikely to help reduce the obstruction that may be worsened by the narcotics (Answer D is incorrect).

10. Answer: C

This patient is receiving 3 g of acetaminophen daily without adequate response, so a change in treatment is indicated. Diclofenac gel may provide adequate relief without systemic adverse effects (Answer C is correct). The patient, who has a history of gastroesophageal reflux disease, is taking aspirin, so naproxen is not preferred (Answer B is incorrect). Evidence indicates that initially GI bleeding is reduced with celecoxib, but this is not maintained with chronic use (Answer A is incorrect). Methylprednisolone injection is more aggressive treatment and may be considered if topical diclofenac is ineffective (Answer D is incorrect).

11. Answer: D

In patients with recurring RA symptoms, moderate disease activity, and the presence of a poor prognostic factor (anti–cyclic citrullinated peptides), adding sulfasalazine and hydroxychloroquine to methotrexate follows guidelines from the 2015 American College of Rheumatology recommendations update for the treatment of RA (Answer D is correct). Specifically, these guidelines recommend either double- or triple-combination DMARD therapy for patients with an inadequate response to methotrexate. Prednisone may be used as bridge therapy, but continued therapy may not be supported by a risk-benefit analysis (Answer A is incorrect). Changing methotrexate from the oral route to the intramuscular route would offer no significant benefit in this case (Answer B is incorrect). Similarly, changing methotrexate to monotherapy with leflunomide would provide no significant benefits (Answer C is incorrect).

12. Answer: C

The allopurinol dose should not be increased at this time because of the presence of a new-onset rash. This may be an adverse effect associated with allopurinol; therefore, allopurinol should be discontinued (Answer A is incorrect). Answer B is incorrect because there is no acute need to restart NSAID therapy at this time because this patient's pain from the acute flare has resolved, and he is not currently experiencing an acute attack. Answer C is correct; trial of a different XAO (e.g., febuxostat) should be initiated in the setting of intolerance or adverse effects before a uricosuric agent is tried. Pegloticase is reserved for patients with a severe gout burden whose disease is refractory to or intolerant of other ULTs (Answer D is incorrect).

Nephrology

John M. Burke, Pharm.D., FCCP, BCPS

St. Louis College of Pharmacy
St. Louis, Missouri

Nephrology

John M. Burke, Pharm.D., FCCP, BCPS

St. Louis College of Pharmacy
St. Louis, Missouri

Learning Objectives

1. Categorize acute kidney injury (AKI) as prerenal, intrinsic, or postrenal on the basis of patient history, physical examination, and laboratory values.
2. Identify risk factors for AKI.
3. Formulate preventive strategies to decrease the risk of AKI in specific patient populations.
4. Formulate a therapeutic plan to manage AKI.
5. Classify the stage or category of either AKI or chronic kidney disease (CKD) on the basis of patient history, physical examination, and laboratory values.
6. Identify risk factors for the progression of CKD.
7. Formulate strategies to slow the progression of CKD.
8. Assess for the presence of common complications of CKD.
9. Develop a care plan to manage the common complications observed in patients with CKD (e.g., anemia, secondary hyperparathyroidism).
10. Interpret results of clinical trials related to the treatment of patients with kidney disease or complications.

Abbreviations in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
ACR	Albumin/creatinine ratio
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
ATN	Acute tubular necrosis
CHF	Congestive heart failure
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease–mineral and bone disorder
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
FENa	Fractional excretion of sodium
GFR	Glomerular filtration rate
HD	Hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
PTH	Parathyroid hormone
RRT	Renal replacement therapy
TSAT	Transferrin saturation

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 75-year-old man (height 73 inches, weight 92.5 kg; baseline serum creatinine [SCr] 0.9 mg/dL) presents to your institution with abdominal pain and dizziness. He has a brief history of gastroenteritis and has had nothing to eat or drink for 24 hours. His blood pressure reading while sitting is 120/80 mm Hg, which decreases to 90/60 mm Hg when standing. His heart rate is 90 beats/minute. His basic metabolic panel shows sodium (Na) 135 mEq/L, chloride (Cl) 108 mEq/L, potassium (K) 4.7 mEq/L, carbon dioxide (CO_2) 26 mEq/L, blood urea nitrogen (BUN) 40 mg/dL, SCr 1.5 mg/dL, and glucose 188 mg/dL. He has no known drug allergies. Which initial treatment of this patient's acute kidney injury (AKI) is best?
   A. Administer furosemide 40 mg intravenously × 1 dose.
   B. Insert Foley catheter to check for residual urine.
   C. Administer fluid bolus (500 mL of normal saline solution).
   D. Administer insulin lispro 3 units subcutaneously.

2. A 44-year-old man is admitted with gram-negative bacteremia. He receives 4 days of parenteral aminoglycoside therapy and develops acute tubular necrosis (ATN). Antibiotic therapy is adjusted on the basis of culture and sensitivity results. Which laboratory value is most consistent with this presentation?
   A. BUN/SCr ratio greater than 20:1.
   B. Urinalysis with no casts visible.
   C. Fractional excretion of sodium (FENa) more than 2%.
   D. Urinary sodium less than 20 mEq/L.

3. A patient with chronic kidney disease (CKD) category G4 (estimated glomerular filtration rate [eGFR] 25 mL/minute/1.73 m^2) has received a diagnosis of gram-positive bacteremia, which is susceptible only to drug X. There are no published reports on how to adjust the dose of drug X in patients with impaired kidney function. Review of

the drug X package insert shows that drug X has significant renal elimination, with 40% excreted unchanged in the urine. The usual dose for drug X is 600 mg/day intravenously and is provided as 100 mg/mL in a 6-mL vial. Which is the best dose (in milliliters of drug X) for this patient?

A. 3.6.

B. 4.1.

C. 4.5.

D. 5.5.

4. A 45-year-old man (weight 59 kg, height 70 inches) has a long history of cancer and malnutrition. His SCr is 0.5 mg/dL. Carboplatin will be initiated, for which an accurate estimate of kidney function is critical. Which group of parameters is best to use when estimating kidney function using the Cockcroft-Gault equation?

A. Actual body weight and measured SCr.

B. Actual body weight and SCr rounded to 1 mg/dL.

C. Ideal body weight and measured SCr.

D. Ideal body weight and SCr rounded to 1 mg/dL.

5. A 59-year-old patient who has had CKD category G5D for 10 years has hypertension, coronary artery disease, mild congestive heart failure (CHF), and type 2 diabetes. Medications are as follows: epoetin 10,000 units intravenously three times/week at dialysis, renal multivitamin once daily, atorvastatin 20 mg/day, insulin, and calcium acetate 1334 mg three times daily with meals. Laboratory values are as follows: hemoglobin (Hgb) 9.2 g/dL, intact parathyroid hormone (iPTH) 300 pg/mL, Na 140 mEq/L, K 4.9 mEq/L, SCr 7.0 mg/dL, calcium 9 mg/dL, albumin 3.5 g/dL, and phosphorus 4.8 mg/dL. His serum ferritin concentration is 80 ng/mL and transferrin saturation (TSAT) is 14%. Mean corpuscular volume, mean corpuscular hemoglobin concentration, and white blood cell count (WBC) are all normal. He is afebrile. Which is best for managing this patient's anemia?

A. Increase epoetin.

B. Add oral iron.

C. Add intravenous iron.

D. Maintain current regimen; patient is at goal.

6. A 60-year-old patient (weight 72 kg) with a history of diabetes and hypertension is in the intensive care unit after having a myocardial infarction about 1 week ago with secondary heart failure. He now has pneumonia. He has been hypotensive for the past 5 days. Before his admission 1 week ago, his SCr was 1.0 mg/dL. His urinary output has steadily been declining for the past 3 days, despite adequate hydration, with 700 mL of urinary output in the past 24 hours. His medications include intravenous dobutamine, nitroglycerin, and cefazolin. Yesterday, his BUN and SCr were 32 and 3.1 mg/dL, respectively; today, they are 41 and 3.9 mg/dL. His urinary osmolality is 290 mOsm/kg. His urinary sodium is 45 mEq/L, and there are tubular cellular casts in his urine. Which type of AKI is this patient most likely experiencing?

A. Prerenal azotemia.

B. ATN.

C. Acute interstitial nephritis (AIN).

D. Hemodynamic/functional-mediated acute kidney injury (AKI).

7. You are evaluating a study comparing epoetin and darbepoetin with respect to their efficacy on mean Hgb concentrations. Both drugs are initiated at the recommended dose, and the Hgb concentration is checked at 4 weeks. Fifty patients are in each group. The mean Hgb in the epoetin group is 12.1 g/dL and is 12.2 g/dL in the darbepoetin group. Which statistical test is best for this comparison?

A. Paired t-test.

B. Independent (unpaired) t-test.

C. Analysis of variance.

D. Chi-square test.

8. A pharmacoeconomic study compared the use of erythropoiesis-stimulating agents with various Hgb concentrations. The primary outcome of this study was cost per quality-adjusted life-year gained. Which best describes this economic evaluation?

A. Cost-minimization.

B. Cost-effectiveness.

C. Cost-benefit.

D. Cost-utility.

9. A 58-year-old woman is being evaluated for AKI. Laboratory test results include serum sodium 134 mEq/L, BUN 35 mg/dL, SCr 1.8 mg/dL, urinary sodium 24 mEq/L, and urinary creatinine 14.3 mg/dL. Which is the best estimate of this patient's FENa?
   A. 0.8%.
   B. 1.25%.
   C. 2.3%.
   D. 4.4%.

10. A 55-year-old man has a history of hypertension. His eGFR is 48 mL/minute/1.73 m^2 and urinary albumin/creatinine ratio (ACR) is 28 mg/g. Which best depicts what this patient's goal blood pressure should be less than, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines?
   A. 130/80 mm Hg.
   B. 140/90 mm Hg.
   C. 140/80 mm Hg.
   D. 130/90 mm Hg.

11. A 66-year-old man has an eGFR of 55 mL/minute/1.73 m^2. His ACR is 100 mg/g. His Hgb is currently 13.2 g/dL, with normal red blood cell indices without treatment. Which best reflects the recommended minimum frequency of Hgb monitoring in this patient?
   A. Monthly.
   B. Every 3 months.
   C. Every 6 months.
   D. Every 12 months.

12. A 68-year-old patient has diabetes, hypertension, and an eGFR of 40 mL/minute/1.73 m^2. Medications include a renal multivitamin once daily, simvastatin, lisinopril, and hydrochlorothiazide. Laboratory values are as follows: Hgb 11.2 g/dL, immunoassay for PTH 200 pg/mL, Na 138 mEq/L, K 4.9 mEq/L, calcium 8.6 mg/dL, albumin 3.5 g/dL, phosphorus 5.8 mg/dL, and 25-hydroxyvitamin D 45 ng/mL. Which is best to prevent CKD–mineral and bone disorder (MBD) in this patient?
   A. Ergocalciferol.
   B. Calcium acetate.
   C. Calcitriol.
   D. Cinacalcet.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Specific Pharmacotherapy
   a. Tasks 1a, 1b, 1c, 1f, 1h, 1k, 2a, 2b, 2d, 3a, 3b, 3c, 3d, 3e
2. Domain 2: Application of Evidence to Practice and Education, Task 2l

Patient Cases

Questions 1–5 pertain to the following case.

A 48-year-old African American man (weight 70 kg) with a history of type 2 diabetes, hypertension, and osteoarthritis is admitted to the intensive care unit after an acute myocardial infarction. He was initially hypotensive, requiring 3 L of intravenous fluid. His blood pressure is now 100/65 mm Hg. Medications before admission include metformin 500 mg orally twice daily, lisinopril 20 mg/day, acetaminophen 650 mg every 6 hours for joint pain, and aspirin 81 mg/daily. Before admission, his kidney function was normal (SCr 1.0 mg/dL); however, during the past 24 hours, his kidney function has declined (BUN 20 mg/dL, SCr 2.1 mg/dL). Serum sodium is 140 mEq/L and serum potassium is 4.4 mEq/L. Urinary volume has been 300 mL over the past 12 hours through urinary catheter. His urine shows muddy casts. His urinary sodium is 45 mEq/L and urinary creatinine is 20 mg/dL. He has edema and pulmonary congestion.

1. Which is the best assessment of this patient's AKI?
   A. KDIGO stage 1 AKI.
   B. KDIGO stage 2 AKI.
   C. KDIGO stage 3 AKI.
   D. Too early to assess for AKI.

2. Which best depicts this patient's FENa?
   A. 0.32%.
   B. 0.67%
   C. 1.5%.
   D. 3.4%.

3. Which is the best classification of this patient's AKI?
   A. Prerenal azotemia.
   B. Intrinsic renal disease.
   C. Postrenal obstruction.
   D. Functional AKI.

4. Which best depicts the medication that could potentially worsen kidney function in this setting and should be discontinued at this time?
   A. Lisinopril.
   B. Nicotine patch.
   C. Acetaminophen.
   D. Aspirin.

5. Which is most appropriate to add at this time?
   A. Intravenous 0.9% sodium chloride.
   B. Hydrochlorothiazide.
   C. Furosemide.
   D. Fluid restriction.

I. ACUTE KIDNEY INJURY OR ACUTE RENAL FAILURE

A. Definitions and Background
   1. AKI is defined as an acute decrease in kidney function or GFR over hours, days, or even weeks and is associated with an accumulation of waste products and (usually) volume.
   2. Criteria and classification of AKI
      a. Definition of AKI according to KDIGO (not graded)
         i. Increase in SCr of 0.3 mg/dL or more within 48 hours; or
         ii. Increase in SCr to 1.5 times baseline or more (baseline known or presumed within prior 7 days); or
         iii. Urinary volume less than 0.5 mL/kg/hour for at least 6 hours
      b. Urinary output classification
         i. Anuric: Less than 50 mL/24 hours; associated with worse outcomes
         ii. Oliguric: Less than 0.5 mL/kg/hour for 12 hours or more
         iii. Nonoliguric: More than 500 mL/24 hours; associated with better patient outcomes and easier to manage because of fewer problems with volume overload
      c. Staging of AKI (Table 1): Can categorize according to risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) categories or into stages 1–3 (AKIN or KDIGO) on the basis of changes in SCr and urinary output

Table 1. Staging of AKI

RIFLE Classification (2004)			AKIN Criteria (2007)		KDIGO Staging (2012)		Common Criteria
	Classification	**SCr or GFR Criteria**	**Stage**	**SCr**	**Stage**	**SCr**	**Urinary Output**
R	Risk of renal dysfunction	SCr increase to 1.5 × baseline *or* GFR decrease > 25%	1	≥ 0.3-mg/dL increase *or* 1.5–2.0 × baseline	1	≥ 0.3-mg/dL increase *or* 1.5–1.9 × baseline	< 0.5 mL/kg/hr for 6–12 hr
I	Injury to kidney	SCr increase to 2 × baseline *or* GFR decrease > 50%	2	2–3 × baseline	2	2.0–2.9 × baseline	< 0.5 mL/kg/hr for ≥ 12 hr
F	Failure of kidney function	SCr increase to 3 × baseline *or* GFR decrease > 75% *or* SCr ≥ 4 mg/dL with acute rise of > 0.5 mg/dL per table in the consensus guideline	3	> 3 × baseline *or* SCr ≥ 4 mg/dL with an acute increase of ≥ 0.5 mg/dL; *or* on RRT	3	≥ 3 × baseline *or* increase to ≥ 4.0 mg/dL *or* Initiation of RRT *or* in patients < 18 yr, decrease in eGFR to < 35 mL/min/1.73 m^2	< 0.3 mL/kg/hr for ≥ 24 hr *or* Anuria for ≥ 12 hr
L	Loss of kidney function	Complete loss of kidney function for > 4 wk					
E	End-stage kidney disease	Complete loss of kidney function for > 3 mo					

AKIN = Acute Kidney Injury Network; RRT = renal replacement therapy.

Information from: Bellomo R, Ronco C, Kellum JA, et al.; the ADQI Workgroup. Acute renal failure – definition, outcome measures, animal models, and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12; Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.

   d. Common complications include fluid overload and acid-base and electrolyte abnormalities.
3. Community-acquired AKI
   a. Low incidence (0.02%) in otherwise healthy patients
   b. As high as 13% incidence among patients with CKD
   c. Usually has a very high survival rate (70%–95%)
   d. Single insult to the kidney, often drug induced
   e. SCr may return to baseline but may lead to development or progression of CKD
4. Hospital-acquired AKI
   a. Has a moderate incidence (2%–5%) and moderate survival rate (30%–50%)
   b. Single or multifocal insults to the kidney
   c. Can still be reversible
5. Intensive care unit–acquired AKI: 5%–6% of patients in intensive care develop AKI during their unit stay, and patients who develop this condition have a low survival rate (10%–30%).
6. Estimating kidney function in AKI
   a. Difficult because commonly used SCr-based equations (Cockcroft-Gault, Modification of Diet in Renal Disease [MDRD], and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) are not appropriate (assume stable SCr)
   b. Equations by Brater and Jelliffe are probably more accurate than the Cockcroft-Gault equation but have not been rigorously tested.
   c. The Chen formula for kinetic eGFR provides a promising, simple method to estimate kidney function when SCr is not stable. Further study is still needed.
   d. If patient is nonoliguric, can calculate creatinine clearance (CrCl) according to a timed urine collection and using the average of SCr samples obtained before and after the urine collection

B. Risk Factors Associated with AKI
1. Preexisting CKD (eGFR less than 60 mL/minute/1.73 m^2)
2. Volume depletion: Vomiting, diarrhea, poor fluid intake, fever, diuretic use, intravascular or effective volume depletion (e.g., CHF, liver disease with ascites)
3. Use of nephrotoxic agents or medications
   a. Intravenous radiographic contrast
   b. Aminoglycosides and amphotericin
   c. Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors
   d. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)
   e. Cyclosporine and tacrolimus
4. Obstruction of the urinary tract

C. Classifications of AKI (Table 2)
1. Prerenal AKI
   a. Initially, the kidney is undamaged.
   b. Characterized by hypoperfusion to the kidney
      i. Systemic hypoperfusion: Hemorrhage, volume depletion, drugs, CHF
      ii. Isolated kidney hypoperfusion: Renal artery stenosis, emboli
   c. Physical examination: Hypotension, signs of volume depletion
   d. Urinalysis will initially be normal (no sediment) but concentrated.
2. Functional AKI
   a. Kidney is undamaged; often classified as prerenal azotemia
   b. Caused by reduced glomerular hydrostatic pressure; often without hypotension
   c. In general, medication-related (cyclosporine, ACEIs and ARBs, and NSAIDs) or seen in patients with low effective blood flow (patients with CHF, patients with liver disease, and older adults) who

cannot compensate for alterations in afferent and efferent tone
   d. Concentrated urine
3. Intrinsic AKI
   a. Kidney is damaged, and damage can be linked to the structure involved: Small blood vessels, glomeruli, renal tubules, and interstitium
   b. Most common cause is ATN; other causes include AIN, vasculitis, and acute glomerulonephritis.
   c. History: Identifiable insult, drug use, infections
   d. Physical examination: Normotensive, euvolemic, or hypervolemic depending on the cause; check for signs of allergic reactions or embolic phenomenon
   e. Urinalysis will reflect damage; urine generally is not concentrated.
4. Postrenal AKI
   a. Kidney is initially undamaged. Bladder outlet obstruction is the most common cause of postrenal AKI. Lower urinary tract obstruction may be caused by calculi. Ureteric obstructions may be caused by clots or intraluminal obstructions. Extrarenal compression can also cause postrenal disease. Elevated intraluminal pressure upstream of the obstruction will result in damage if the obstruction is not relieved.
   b. History: Trauma, benign prostatic hyperplasia, cancers
   c. Physical examination: Distended bladder, enlarged prostate
   d. Urinalysis may be nonspecific.
   e. Radiography or ultrasonography may reveal hydronephrosis and help identify obstruction.

Table 2. Classifications of AKI

	Prerenal and Functional	**Intrinsic (ATN and AIN)**	**Postrenal**
History and clinical presentation	Volume depletion Renal artery stenosis CHF Hypercalcemia NSAID, ACEI, and ARB use Cyclosporine	Longstanding renal hypoperfusion Nephrotoxins (e.g., contrast or antibiotics) Vasculitis Glomerulonephritis	Kidney stones BPH Cancers
Physical examination	Hypotension Dehydration Petechia if thrombotic Ascites	Rash, fever (with AIN) Persistent hypotension	Distended bladder Enlarged prostate
Serum BUN/SCr ratio	> 20:1	10–15:1	10–15:1
Urinary sodium	< 20 mEq/L	> 40 mEq/L	> 40 mEq/L
FENa	< 1%	> 2%	> 2%
Urinary osmolality	High urine osmolality	Low urine osmolality	Low urine osmolality
Urinary sediment	Normal	Muddy brown granular casts; tubular epithelial casts	Variable; may be normal
Urinary WBC	Negative	2–4+	Variable
Urinary RBC	Negative	2–4+	1+
Proteinuria	Negative	Positive	Negative

ACEI = angiotensin-converting enzyme inhibitor; AIN = acute interstitial nephritis; ARB = angiotensin II receptor blocker; ATN = acute tubular necrosis; BPH = benign prostatic hypertrophy; CHF = congestive heart failure; FENa = fractional excretion of sodium; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cell count.

5. Calculation of fractional excretion of sodium (FENa − percentage of Na filtered at the glomerulus that is excreted in the urine)

$$\text{FENa (\%)} = \frac{\text{(urinary sodium)/(serum sodium)}}{\text{(urinary creatinine)/(SCr)}} \times 100$$

D. Prevention of AKI
   1. Avoid nephrotoxic drugs, when possible.
   2. Ensure adequate hydration.
   3. Educate patient.
   4. Use drug therapies to decrease the incidence of contrast-induced nephropathy (see section II, "Drug-Induced Kidney Damage").

E. Treatment and Management of Established AKI
   1. Prerenal azotemia: Correct primary hemodynamics.
      a. Intravenous normal saline or lactated Ringer solution, if volume depleted
      b. Blood pressure management, if needed
      c. Blood products, if needed
      d. Hold or discontinue medications that affect renal hemodynamics (i.e., ACEIs, ARBs, NSAIDs).
   2. Intrinsic: No specific therapy universally effective
      a. Eliminate the causative hemodynamic abnormality or toxin.
      b. Avoid additional insults.
      c. Manage fluid and electrolytes to prevent volume depletion or overload and electrolyte imbalances.
      d. Nutrition support is important, but no specific recommendations are widely accepted.
      e. Medical therapy recommendations according to the KDIGO guidelines
         i. Loop diuretics: Recommend not using to prevent AKI (grade 1B) and suggest not using to treat AKI, except to manage hypervolemia (grade 2C)
         ii. Therapeutic agents (e.g., dopamine, nesiritide, fenoldopam, mannitol) are not indicated in AKI management and may be harmful for the patient.
   3. Postrenal AKI: Relieve obstruction. Early identification is important. Consult urology or radiology.
   4. Indications for renal replacement therapy (RRT) in AKI
      a. BUN greater than 100 mg/dL or signs of uremia (e.g., encephalopathy, pericarditis)
      b. Volume overload unresponsive to diuretics
      c. Life-threatening electrolyte imbalance: Hyperkalemia, hypermagnesemia
      d. Refractory metabolic acidosis

Patient Cases

6. A 67-year-old man is referred for intermittent chest pain. His medical history is significant for CKD KDIGO category G3a, type 2 diabetes, and hypertension. Medications include enalapril, hydrochlorothiazide, and pioglitazone. Laboratory values include SCr 1.8 mg/dL, glucose 189 mg/dL, Hgb 12 g/dL, and hematocrit (Hct) 36%. His physical examination is normal. The treatment plan is elective cardiac catheterization. Which is best for hydration?
   A. 0.9% sodium chloride.
   B. 0.45% sodium chloride.
   C. 5% dextrose/0.45% sodium chloride.
   D. Oral hydration with water.

7. After the administration of radiocontrast, which best represents the optimal time to reevaluate renal function to assess for the development of contrast-associated nephropathy?
   A. 6 hours.
   B. 24 hours.
   C. 4 days.
   D. 7 days.

II. DRUG-INDUCED KIDNEY DAMAGE

A. Introduction: Drugs can cause kidney damage through many mechanisms. Evaluate potential drug-induced nephropathy on the basis of the period of ingestion, patient risk factors, and the propensity of the suspected agent to cause kidney damage.
   1. Risk factors
      a. History of CKD
      b. Advanced age
   2. Epidemiology
      a. 7% of all drug toxicities
      b. 18%–27% of AKI in hospitals
      c. 1%–5% of NSAID users in community
      d. Most implicated medications: Aminoglycosides, NSAIDs, ACEIs, intravenous contrast dye, amphotericin
   3. The kidneys are at elevated risk of toxic injury because:
      a. High exposure to toxin: Kidney receives 20%–25% cardiac output.
      b. Autoregulation and specialized blood flow through glomerulus
      c. High intrarenal drug metabolism
      d. Tubular transport processes
      e. Concentration of solutes (i.e., toxins) in tubules
      f. High energy requirements of tubule epithelial cells
      g. Urine acidification
   4. Pseudo-nephrotoxicity
      a. Drugs that inhibit the tubular secretion of creatinine: Trimethoprim, cimetidine
      b. Drugs that increase BUN: Corticosteroids, tetracycline
      c. Drugs that interfere with the creatinine assay: Cefoxitin and other cephalosporins

B. Acute Tubular Necrosis
   1. Most common drug-induced kidney disease in the inpatient setting
   2. Aminoglycoside nephrotoxicity
      a. Incidence: 1.7%–58% of patients
      b. Pathogenesis
         i. Caused by proximal tubular damage leading to obstruction of the lumen
         ii. Cationic charge of drug leads to binding to tubular epithelial cells and uptake into those cells.
         iii. Accumulation of phospholipids and toxicity
      c. Presentation
         i. Gradual rise in SCr concentrations and decrease in GFR after 6–10 days of therapy
         ii. Patients usually have nonoliguric kidney failure.
         iii. Wasting of electrolytes (i.e., hypokalemia and hypomagnesemia) may occur.
      d. Risk factors
         i. Related to dosing: Large total cumulative dose, prolonged therapy, trough concentration exceeding 2 mg/L, recent previous aminoglycoside therapy
         ii. Concurrent use of other nephrotoxins (cyclosporine, amphotericin B, diuretics, vancomycin)
         iii. Patient related: Preexisting kidney disease or damage, advanced age, poor nutrition, shock, gram-negative bacteremia, liver disease, hypoalbuminemia, obstructive jaundice, dehydration, and K and magnesium deficiencies
      e. Prevention
         i. Avoid use in high-risk patients.
         ii. Maintain adequate hydration.
         iii. Limit the total cumulative aminoglycoside dose.
         iv. Avoid use of other nephrotoxins.
         v. Use extended-interval (once daily) dosing; monitor these and other high-risk patients closely.
   3. Radiographic contrast media nephrotoxicity related to intravenous contrast use
      a. Incidence
         i. Third leading cause of inpatient AKI
         ii. Less than 2% and up to 50% of patients, depending on risk
         iii. Associated with a high (34%) in-hospital mortality rate
         iv. Commonly used in procedures such as contrast-enhanced computed tomography (CT), cardiac catheterization, angiography, and venography
      b. Pathogenesis
         i. Renal ischemia caused by alteration in intrarenal hemodynamics
            (a) Osmotic diuresis and dehydration. Contrast media based on osmolality:
               (1) High-osmolar contrast media about 2000 mOsm/kg
               (2) Low-osmolar contrast media 600–800 mOsm/kg
               (3) Iso-osmolar contrast media 290 mOsm/kg
            (b) Some contrast agents also cause systemic hypotension on injection and renal vasoconstriction caused by the release of adenosine, endothelin, and other vasoconstrictors.
         ii. Direct tubular toxicity caused by reactive oxygen species; directly influenced by tubular flow rates and duration of exposure of tubules
      c. Presentation
         i. Initial transient osmotic diuresis, followed by tubular proteinuria
         ii. SCr rises within 24 hours and peaks 2–5 days after the procedure.
         iii. 50% of patients develop oliguria, and some will need dialysis.

d. Risk factors for toxicity
    i. Preexisting kidney disease (SCr more than 1.5 mg/dL or CrCl less than 60 mL/minute/1.73 m^2)
    ii. Diabetes mellitus
    iii. Volume depletion
    iv. Age 75 and older
    v. Anemia
    vi. Conditions with decreased blood flow to the kidney (e.g., CHF)
    vii. Hypotension
    viii. Other nephrotoxins
    ix. Large doses of contrast (more than 140 mL) or hyperosmolar contrast agents
e. Prevention
    i. Volume expansion with either intravenous isotonic saline or sodium bicarbonate (KDIGO recommendation, grade 1A) beginning 6–12 hours before the procedure; maintain urinary output greater than 150 mL/hour. Recent data analyses from the PRESERVE trial suggested no added benefit on short-term AKI or long-term outcomes from the use of intravenous sodium bicarbonate compared with isotonic saline (N Engl J Med 2018;378:603-14).
    ii. Use an alternative imaging study, if possible.
    iii. Discontinue nephrotoxic agents and avoid diuretics.
    iv. Use low-osmolar or iso-osmolar contrast agents in patients at risk (KDIGO recommendation, grade 1B).
    v. Medications used to prevent contrast-induced nephropathy
        (a) Acetylcysteine: Antioxidant and vasodilatory mechanism. Accumulation of glutathione takes time, so it may not be as effective in emergencies. Various dosing recommendations. Widely used. Considered safe. May use oral acetylcysteine in combination with intravenous hydration (KDIGO suggestion, grade 2D). Recent studies suggest no additional benefit over intravenous hydration (PRESERVE trial: N Engl J Med 2018;378:603-14 and ACT: Circulation 2011;124:1250-9).
        (b) Ascorbic acid: Antioxidant. One large study showed benefit when used immediately before. Not confirmed. Give oral ascorbic acid 3 g before procedure and 2 g twice daily for two doses after procedure. May play a role in emergencies
        (c) Theophylline: Do not use (KDIGO suggestion, grade 2C).
        (d) Fenoldopam: Do not use (KDIGO recommendation, grade 1B).
        (e) Prophylactic hemodialysis (HD) and hemofiltration: Do not use (KDIGO suggestion, grade 2C).
f. Joint Commission standards on medication management regarding radiologic contrast media
    i. Treated as a drug
    ii. Subject to all the standards for medication management in a health system
g. Nephrogenic systemic fibrosis (a.k.a. nephrogenic fibrosing dermopathy)
    i. Rare but associated with gadolinium-based agents used in high doses for magnetic resonance imaging/angiogram
    ii. Occurs in patients with moderate CKD to end-stage renal disease (ESRD) given intravenous contrast, and systemic acidosis seems to be a risk factor
    iii. Although gadolinium does not cause AKI, it is considered inappropriate for use in patients with AKI or CKD.
    iv. Onset 2–18 days after exposure
    v. Presents as burning; itching; swelling, hardening, or tightening of skin; skin patches; spots on eyes; joint stiffness; and muscle weakness

vi. Can cause organ damage, and deaths have occurred
vii. In 2010, the U.S. Food and Drug Administration (FDA) required the addition of a warning to prescribing information.

4. Cisplatin nephrotoxicity
   a. Incidence: 6%–13% with appropriate dosing and administration
   b. Pathogenesis: Complex; direct tubular toxin
   c. Presentation
      i. SCr peaks 10–12 days after therapy begins but may continue to rise with subsequent cycles of therapy.
      ii. Renal magnesium wasting is common (may be severe with central nervous system symptoms) and may be accompanied by hypokalemia and hypocalcemia.
      iii. May result in irreversible kidney damage
   d. Risk factors for toxicity: Many courses of cisplatin, advanced patient age, dehydration, concurrent nephrotoxins, kidney irradiation, alcohol abuse
   e. Prevention
      i. Avoid concurrent use of nephrotoxins.
      ii. Use smallest dose possible and decrease frequency of administration.
      iii. Aggressive intravenous hydration: 1–4 L within 24 hours of high-dose cisplatin
      iv. Amifostine: Cisplatin-chelating agent may be considered in patients at risk of nephrotoxicity
      v. Alternative platinum analogs (i.e., carboplatin or oxaliplatin) can be used in patients at high risk of nephrotoxicity.
5. Amphotericin B nephrotoxicity
   a. Incidence
      i. Increases as cumulative dose increases
      ii. Approaches 80% with cumulative doses of 4 g or more
   b. Pathogenesis
      i. Direct proximal and distal tubular toxicity
      ii. Arterial vasoconstriction
   c. Presentation
      i. Manifests after administration of 2–3 g
      ii. Loss of tubular function leads to electrolyte wasting (especially K^+, Na^+, and Mg^{2+}) and distal tubular acidosis.
      iii. Patients may need substantial K^+ and Mg^{2+} replacement.
      iv. SCr increases and GFR decreases because of a decrease in kidney blood flow from vasoconstriction caused by amphotericin.
   d. Risk factors for toxicity: Existing kidney dysfunction, high average daily doses, diuretic use, volume depletion, concomitant nephrotoxins, rapid infusion
   e. Prevention
      i. Avoid other nephrotoxins (especially cyclosporine) and limit the total cumulative dose.
      ii. Intravenous hydration with 0.9% sodium chloride at least 1 L/day before each dose
      iii. Use a liposomal product in high-risk patients.

C. Functional (Hemodynamically Mediated) AKI
   1. Caused by a decrease in intraglomerular pressure through the vasoconstriction of afferent arterioles or the vasodilation of efferent arterioles
   2. ACEIs and ARBs
      a. Pathogenesis
         i. Vasodilation of the efferent arteriole
         ii. Leads to a decrease in glomerular hydrostatic pressure and a resultant decrease in GFR

b. Presentation
    i. Exerts a predictable dose-related reduction in GFR
    ii. SCr is usually expected to rise by up to 30%.
        (a) Usually occurs within 2–5 days
        (b) Usually stabilizes in 2–3 weeks
        (c) Increases greater than 30% may be harmful.
        (d) Usually reversible on drug discontinuation
c. Risk factors for toxicity: Patients with bilateral (or unilateral with a solitary kidney) renal artery stenosis, decreased effective kidney blood flow (CHF, cirrhosis), preexisting kidney disease, and volume depletion
d. Prevention
    i. Initiate therapy with low doses and gradually titrate.
    ii. Change to long-acting agents once tolerance is established.
    iii. Initially, monitor kidney function and SCr concentrations daily for inpatients and weekly for outpatients.
    iv. Avoid concomitant use of diuretics, if possible, during therapy initiation.
    v. Avoid concomitant use of NSAIDs.

3. NSAIDs
    a. Incidence: Estimates indicate that 500,000–2.5 million people develop NSAID-induced nephrotoxicity annually in the United States.
    b. Pathogenesis
        i. Vasodilatory prostaglandins help maintain glomerular hydrostatic pressure by afferent arteriolar dilation, especially in times of decreased kidney blood flow.
        ii. NSAID administration in the setting of decreased kidney perfusion reduces this compensatory mechanism by decreasing the production of prostaglandins, resulting in afferent vasoconstriction and reduced glomerular blood flow.
    c. Presentation
        i. Can occur within days of starting therapy
        ii. Patients generally have low urinary volume and Na; may also have an increase in BUN, SCr, K^+, edema, and weight
    d. Risk factors for toxicity: Preexisting kidney disease, systemic lupus erythematosus, high plasma renin activity (e.g., CHF, hepatic disease), diuretic therapy, atherosclerotic disease, and advanced age
    e. Prevention
        i. Use therapies other than NSAIDs, when appropriate (e.g., acetaminophen for osteoarthritis).
        ii. COX-2–specific inhibitors have not been shown to cause less kidney dysfunction, and they increase cardiovascular complications.
    f. Treatment
        i. If NSAID-induced AKI is suspected, discontinue drug and give supportive care.
        ii. Avoid concomitant use of medications affecting the renin-angiotensin-aldosterone system.
        iii. Recovery is usually rapid.

4. Cyclosporine and tacrolimus
    a. Incidence
        i. 5-year risk of developing CKD after transplantation of a nonrenal organ is 7%–21%.
        ii. Occurrence of kidney failure in the transplant recipient population increases the risk of death by 4-fold.

b. Pathogenesis
    i. Caused by a dose-related hemodynamic mechanism; calcineurin inhibitors may also cause chronic interstitial nephritis through a separate mechanism that is not dose related
    ii. Causes vasoconstriction of afferent arterioles through possible increased activity of various vasoconstrictors (thromboxane A_2, endothelin, sympathetic nervous system) or decreased activity of vasodilators (nitric oxide, prostacyclin)
    iii. Increased vasoconstriction from angiotensin II may also contribute.
    iv. Effects usually resolve with a dose reduction.
c. Presentation
    i. Can occur within days of starting therapy
    ii. SCr rises and eGFR decreases.
    iii. Patients often have hypertension, hyperkalemia, and hypomagnesemia.
    iv. A biopsy is often needed for kidney transplant recipients to distinguish drug-induced injury from acute allograft rejection.
d. Risk factors for toxicity include advanced age, high initial cyclosporine dose, kidney graft rejection, hypotension, infection, and concomitant nephrotoxins.
e. Prevention
    i. Monitor serum cyclosporine and tacrolimus concentrations closely.
    ii. Use lower doses in combination with other nonnephrotoxic immunosuppressants (e.g., steroids, mycophenolate mofetil).
    iii. Calcium channel blockers *may* help antagonize the vasoconstrictor effects of cyclosporine by dilating afferent arterioles.

D. Tubulointerstitial Disease
1. Involves the renal tubules and the surrounding interstitium
2. Onset can be acute or chronic.
    a. Acute onset generally involves interstitial inflammatory cell infiltrates, rapid loss of kidney function, and systemic symptoms (i.e., fever and rash).
    b. Chronic onset shows interstitial fibrosis, slow decline in kidney function, and no systemic symptoms.
3. Acute allergic interstitial nephritis
    a. Cause of up to 3% of all AKI cases; caused by an allergic hypersensitivity reaction that affects the interstitium of the kidney
    b. Many medications and medication classes can cause this type of kidney failure, including β-lactams and NSAIDs (although the presentations are different).
        i. Penicillins: Classic presentation of acute allergic interstitial nephritis. Signs and symptoms occur about 1–2 weeks after therapy initiation and include fever, maculopapular rash, eosinophilia, pyuria, hematuria, and proteinuria. Eosinophiluria may also be present.
        ii. NSAIDs: Onset much more delayed; typically begins about 6 months into therapy. Usually occurs in older adults receiving chronic NSAID therapy. Patients do not usually have systemic symptoms.
    c. Kidney biopsy may be needed to confirm the diagnosis.
    d. Treatment includes discontinuing the offending agent and possibly initiating steroid therapy.
4. Chronic interstitial nephritis
    a. Often progressive and irreversible
    b. Lithium
        i. Toxicity results from a duration-related decrease in response to antidiuretic hormone after long-term use (more than 10 years of therapy).

ii. Clinical presentation
(a) Often asymptomatic, with slow progression over years
(b) May be recognized by slow increases in blood pressure or BUN and SCr
iii. Risks include long duration of use, elevated serum concentrations, and repeated episodes of AKI from lithium toxicity.
iv. Prevention is accomplished by maintaining the lowest serum lithium concentrations possible, avoiding dehydration, and monitoring kidney function closely.
c. Cyclosporine and tacrolimus: Presents later in therapy (about 6–12 months) than hemodynamically mediated toxicity

5. Papillary necrosis
a. Form of chronic interstitial nephritis affecting the papillae, causing necrosis of the collecting ducts
b. Results from the long-term use of analgesics
i. "Classic" example was with products that contained phenacetin.
ii. Occurs more often with combination products
iii. Products containing caffeine may also increase risk.
c. Evolves slowly as time progresses
d. Affects women more often than men
e. Difficult to diagnose, and much controversy remains about risk, prevention, and cause

E. Postrenal (Obstructive) Nephropathy
1. Results from obstruction of the flow of urine after glomerular filtration
2. Renal tubular obstruction
a. Caused by intratubular precipitation of tissue degradation products or precipitation of drugs or their metabolites
i. Tissue degradation products
(a) Uric acid intratubular precipitation after tumor lysis after chemotherapy
(b) Drug-induced rhabdomyolysis leading to intratubular precipitation of myoglobin
(c) Results in rapid decline in kidney function, with resultant oliguric or anuric kidney failure
ii. Drug precipitation: Sulfonamides, methotrexate, acyclovir, ascorbic acid; needlelike crystals observed in leukocytes found on urinalysis can prompt diagnosis
b. Prevention includes pretreatment hydration, maintenance of high urinary volume, and alkalinization of the urine.
3. Extrarenal urinary tract obstruction
a. Benign prostatic hypertrophy can be worsened by anticholinergics.
b. Bladder outlet or ureteral obstruction from fibrosis after cyclophosphamide for hemorrhagic cystitis
4. Nephrolithiasis
a. Usually does not affect GFR, so does not have the classic signs and symptoms of nephrotoxicity
b. Some medications contribute to the formation of kidney stones: triamterene, sulfadiazine, indinavir, and ephedrine derivatives.

F. Glomerular Disease
1. Proteinuria is the hallmark of glomerular disease and may occur with or without a decrease in GFR.
2. A few distinct drugs can cause glomerular disease.
a. NSAIDs: Associated with acute allergic interstitial nephritis
b. Heroin: Can be caused by direct toxicity or toxicity from additives or infection from injection, and ESRD develops in most cases
c. Parenteral gold: Results from immune complex formation along glomerular capillary loops

III. CHRONIC KIDNEY DISEASE

A. Background
   1. Prevalence: According to the 2018 U.S. Renal Data System Annual Report, 14.8% of adults (20 years and older) in the National Health and Nutrition Examination Survey population (2013–2016) have CKD. There were 450,887 patients on dialysis in 2016 and 209,854 transplant recipients. Incidence rate is flat, so growth in the number of patients with ESRD results mainly from the longer life span of these patients.
   2. Definition of CKD
      a. According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), CKD is kidney damage for more than 3 months, as defined by structural or functional abnormality of the kidney, with or without decreased GFR. Manifested by either pathologic abnormalities or markers of kidney damage – including albuminuria, abnormal urine sediment, serum electrolyte abnormalities, abnormal histology, or abnormalities in imaging tests – *or* GFR less than 60 mL/minute/1.73 m^2 for 3 months, with or without kidney damage (Table 3)

Table 3. KDOQI Stages in CKD

Stage of Renal Disease	Damage	GFR (mL/min/1.73 m^2)
Increased risk of developing kidney disease	Risk factors for CKD (diabetes, HTN, family history)	≥ 90
Stage 1	Kidney damage with normal GFR	≥ 90
Stage 2	Kidney damage with mild decrease in GFR	60–89
Stage 3	Moderate decrease in GFR	30–59
Stage 4	Severe decrease in GFR	15–29
Stage 5	Kidney failure	< 15

CKD = chronic kidney disease; HTN = hypertension.

      b. According to the KDIGO clinical practice guideline for the evaluation and management of CKD, CKD is defined as abnormalities in kidney structure or function for more than 3 months. These abnormalities may be seen as persistent markers of kidney damage or GFR less than 60 mL/minute/1.73 m^2 (Table 4).

Table 4. KDIGO Categories in CKD

GFR Category	Terms	GFR (mL/min/1.73 m^2)
G1	Kidney damage with normal or high GFR	≥ 90
G2	Kidney damage with mildly decreased GFR	60–89
G3a	Mildly to moderately decreased GFR	45–59
G3b	Moderately to severely decreased GFR	30–44
G4	Severely decreased GFR	15–29
G5	Kidney failure	< 15

B. Etiology
   1. Diabetes (45% of new cases of ESRD in the United States)
   2. Hypertension (28% of new cases)
   3. Glomerulonephritis (7.4%)
   4. Others: Urinary tract disease, polycystic kidney disease, lupus, analgesic nephropathy, unknown

C. Risk Factors
   1. Susceptibility (associated with an increased risk but not proven to cause CKD): Advanced age, reduced kidney mass, low birth weight, racial or ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia; mostly not modifiable
   2. Initiation (directly cause CKD): Diabetes, hypertension, autoimmune disease, polycystic kidney diseases, and drug toxicity; may be modifiable by drug therapy
   3. Progression (result in faster decline in kidney function): Hyperglycemia, elevated blood pressure, proteinuria, and smoking

Patient Cases

Questions 8–11 pertain to the following case.

A 55-year-old man has a history of hypertension and newly diagnosed type 2 diabetes. He denies alcohol use but does smoke cigarettes (1 pack/day). His medications include atenolol 50 mg/day and a multivitamin. At your pharmacy, his blood pressure is 149/92 mm Hg. His ACR is 400 mg/g. A recent SCr is 1.9 mg/dL, which is consistent with a value measured 3 months earlier. His eGFR is 50 mL/minute/1.73 m^2.

8. Which category best reflects his kidney disease, according to the KDIGO criteria?
   A. G2.
   B. G3a.
   C. G3b.
   D. G4.

9. Using the KDIGO categorization, which best assesses this patient's albuminuria?
   A. Category A1.
   B. Category A2.
   C. Category A3.
   D. Nephrotic-range proteinuria.

10. Assuming that nonpharmacologic approaches have been optimized, which is best to limit the progression of his kidney disease?
   A. Add nifedipine.
   B. Add diltiazem.
   C. Add enalapril.
   D. Increase atenolol.

11. Enalapril is added to this patient's regimen. Two weeks later, he returns for a follow-up. His blood pressure is 139/89 mm Hg. A repeat SCr is 2.3 mg/dL, and serum potassium is 5.2 mEq/L. Which is the best recommendation for this patient?
   A. Add chlorthalidone 50 mg/day. Monitor blood pressure, SCr, and K in 2 weeks.
   B. Change enalapril to diltiazem extended release. Monitor blood pressure, SCr, and K in 2 weeks.
   C. Change enalapril to valsartan.
   D. Increase atenolol.

Patient Cases *(Cont'd)*

12. A study compared use of an ARB alone and in combination with an ACEI in patients with CKD. Acute kidney injury occurred in 80 of 724 patients (11%) receiving monotherapy and 130 of 724 patients (18%) receiving combination therapy. Given this information, which most accurately depicts the number of patients needed to harm?

    A. 7.

    B. 14.

    C. 50.

    D. 105.

D. Albuminuria or Proteinuria

1. Marker of kidney damage, progression factor, and cardiovascular risk factor. Can be classified as in Table 5

Table 5. KDIGO Categories of Albuminuria

Category	Classification[a]	ACR (mg/g)	Daily Excretion (mg/24 hr)
A1	Normal to mildly increased	< 30	< 30
A2	Moderately increased	30–300	30–300
A3	Severely increased albuminuria	> 300	> 300
	Nephrotic-range proteinuria		> 3000

[a]Note: Classified as "normal" or "increased urinary albumin excretion" in American Diabetes Association. Diabetes Care 2016;39(suppl 1): S72-S80.

ACR = albumin/creatinine ratio.

2. Assessment for proteinuria: Usually assessed by measuring urinary ACR. Spot urine: Untimed sample is adequate for adults and children (screening test). A timed (24-hour) urine collection may be used to quantify severe proteinuria.

E. Assessment of Kidney Function

1. Serum creatinine (SCr)
    a. Avoid use as the sole assessment of kidney function.
    b. Depends on age, sex, weight, and muscle mass
    c. All laboratories now use "standardized" SCr traceable to isotope dilution mass spectrometry, which decreases variability in results between laboratories.
2. Measurement of GFR: Inulin, iothalamate, and others are very rarely used in clinical practice.
3. Measurement of CrCl through urine collection
    a. Reserve for vegetarians, patients needing dietary assessment, or those with abnormal muscle mass (e.g., patients with low muscle mass, patients with amputations) or when documenting the need to start or continue dialysis.
    b. Urine collection yields a better estimate in patients with very low muscle mass.
    c. In most cases, equations overestimate kidney function because SCr concentrations are low in patients with very low muscle mass.
4. Estimated CrCl using the Cockcroft-Gault equation (mL/minute): Overestimates GFR because of tubular secretion of creatinine

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{body weight } (\times 0.85 \text{ if female})}{\text{SCr} \times 72}$$

Although actual body weight was used in the original publication, either ideal body weight or adjusted body weight is often used instead.

5. eGFR with MDRD study data equation
   a. eGFR (mL/minute/1.73 m^2) in patients with known CKD (not accurate in patients with a GFR greater than 60 mL/minute/1.73 m^2 or less accurate in patient populations without kidney disease)
   b. Isotope dilution mass spectrometry–traceable four-variable MDRD formula correlates well with the original MDRD formula; simpler to use:

$$\text{eGFR (mL/minute/1.73 m}^2) = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} (\times 0.742 \text{ if female}) (\times 1.212 \text{ if African American})$$

   c. This equation is available at www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx (accessed September 1, 2020) or www.kidney.org.
6. CKD-EPI equation: Alternative equation based on race, sex, SCr range, and age. More accurate than MDRD at GFR values greater than 60 mL/minute/1.73 m^2. Available at https://www.kidney.org/content/ckd-epi-creatinine-equation-2009 (accessed September 1, 2020).
7. For children, use the modified Schwartz "bedside" formula; see https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/children-conventional-unit/Pages/default.aspx (accessed September 1, 2020).

F. Diabetic Kidney Disease
   1. Pathogenesis
      a. Hypertension (systemic and intraglomerular)
      b. Glycosylation of glomerular proteins
      c. Genetic links
   2. Diagnosis
      a. Long history of diabetes
      b. Proteinuria
      c. Retinopathy often coexists, suggestive of microvascular disease.
   3. Monitoring
      a. Type 1 diabetes: Begin annual monitoring for albuminuria 5 years after diagnosis.
      b. Type 2 diabetes: Begin annual monitoring for albuminuria immediately (do not know how long patient has had diabetes mellitus).
   4. Management and slowing progression
      a. Aggressive blood pressure management (Table 6)

Table 6. Goal Blood Pressure Readings in Patients with Diabetes

Group	Severity of Albuminuria	Goal Blood Pressure (maximum)	Level of Evidence
ADA 2020	Any	140/90 mm Hg[a]	A
KDIGO	Normal to mild albuminuria	140/90 mm Hg	1B
KDIGO	Moderate to severe albuminuria	130/80 mm Hg	2D
HBP 2017	Any	130/80 mm Hg	

[a]Systolic blood pressure < 130 mm Hg and diastolic blood pressure < 80 mm Hg may be appropriate in some patients.

ADA = American Diabetes Association; HBP = High Blood Pressure Clinical Practice Guidelines 2017.

i. Either ACEIs or ARBs are preferred and should be used with any degree of proteinuria, even if the patient is not hypertensive.
   (a) Use moderate to high doses with proteinuria.
   (b) Hold ACEI or ARB if serum potassium is greater than 5.6 mEq/L or if SCr increases by more than 30% after initiation. Potassium binders such as patiromer can be considered for chronic management of hyperkalemia.
   (c) Increased risk of hyperkalemia if combined with direct renin inhibitor
ii. Most patients will need diuretic in combination (thiazide with stages 1–3 and loop diuretics in stages 4 and 5). If blood pressure is greater than 160/100 mm Hg, begin with a two-drug regimen.
iii. Calcium channel blockers (nondihydropyridine) are second line to ACEIs and ARBs. Data are emerging for combined therapy.
iv. Dietary sodium consumption should be less than 2.4 g/day. Modify the Dietary Approaches to Stop Hypertension (DASH) diet to limit K intake as well.

b. Intensive blood glucose control. Glycosylated hemoglobin (A1C) less than 7%. Less aggressive with more advanced CKD
c. Protein restriction: Data are insufficient in adults with diabetes, but 0.8 g/kg/day may slightly reduce progression in stage 4 or 5 CKD and decrease the risk of ESRD. Patients should avoid high-protein diets (greater than 1.3 g/kg/day).

G. Nondiabetic Nephropathy
   1. Management of hypertension
      a. Blood pressure goals: 2017 High Blood Pressure Clinical Practice Guidelines: Patients 18 years and older with hypertension and CKD: Goal blood pressure less than 130/80 mm Hg (Table 7)

Table 7. KDIGO Blood Pressure Goals

Target Group	Severity of Albuminuria	Goal Blood Pressure (maximum)	Level of Evidence
Nondiabetic CKD	Normal to mild albuminuria	140/90 mm Hg	1B
Nondiabetic CKD	Moderate to severe albuminuria	130/80 mm Hg	2D moderate 2C severe

      b. If proteinuric and hypertensive, use ACEI *or* ARB. Often need to add (or begin with) combination. Diuretic or calcium channel blocker can be added as a second drug. Monitor serum potassium.
   2. Minimize protein in diet. Controversial. May slow progression according to MDRD study but may also impair nutrition. Very low-protein diet may increase mortality.

H. Other Guidelines to Slow Progression
   1. Hyperlipidemia
      a. Assessment
         i. Newly identified CKD: Recommend evaluation of lipid profile (KDIGO, grade 1C) (Table 8).
         ii. Follow-up measurement of lipid concentrations not necessary for most patients (not graded)
      b. Treatment recommendations (KDIGO)

Table 8. KDIGO Lipid Treatment Guidelines

Target Group	Treatment Recommendation	Grade
Adults ≥ 50 yr, GFR category G1–G2	Statin	1B
Adults ≥ 50 yr, GFR category G3a–G5	Statin or statin/ezetimibe	1A
Adults 18–49 yr with CKD before dialysis or transplant with CAD, diabetes, stroke, or estimated risk of coronary death or MI > 10%	Statin	2A
Adults on therapy when dialysis initiated	Continue statin or statin/ezetimibe	2C
Adults with dialysis-dependent CKD	Do *not* start therapy	2A
Adult kidney transplant recipients	Statin	2A

CAD = coronary artery disease; MI = myocardial infarction.

Information from: Wanner C, Tonelli M; KDIGO Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85:1303-9.

2. Smoking cessation

Patient Cases

13. A 70-year-old man is being assessed for HD access. He has a history of diabetes mellitus and hypertension but is otherwise healthy. Which HD access modality is best to use in this patient?
    A. Subclavian catheter.
    B. Tenckhoff catheter.
    C. Arteriovenous graft.
    D. Arteriovenous fistula.

14. A patient undergoing long-term HD has intradialytic hypotension. After nonpharmacologic approaches have been optimized, which medication is best to manage his low blood pressure?
    A. Levocarnitine.
    B. Sodium chloride tablets.
    C. Fludrocortisone.
    D. Midodrine.

15. A patient with CKD on peritoneal dialysis presents with fever and abdominal pain. She also notes that her peritoneal dialysate has become cloudy. Laboratory evaluation of dialysate reveals many white blood cells, primarily neutrophils. Gram stain and culture of the fluid are ordered. According to the 2016 recommendations for peritoneal dialysis–related peritonitis, which is the best empiric therapy for this patient?
    A. Intravenous metronidazole plus gentamicin.
    B. Intravenous clindamycin plus vancomycin.
    C. Cefazolin plus ceftazidime instilled intraperitoneally.
    D. Vancomycin instilled intraperitoneally.

IV. RENAL REPLACEMENT THERAPY

A. Indications for RRT
   1. A: Acidosis (not responsive to bicarbonate)
   2. E: Electrolyte abnormality (hyperkalemia, hyperphosphatemia)
   3. I: Intoxication (boric acid, ethylene glycol, lithium, methanol, phenobarbital, salicylate, theophylline)
   4. O: Fluid overload (symptomatic [pulmonary edema])
   5. U: Uremia (pericarditis and weight loss)

B. Two Primary Modes of Dialysis
   1. Hemodialysis: Most common modality in United States
   2. Peritoneal dialysis

C. Hemodialysis (intermittent for ESRD)
   1. Access
      a. Arteriovenous fistula: Preferred access
         i. Natural, formed by anastomosis of artery and vein
         ii. Lowest incidence of infection and thrombosis, lowest cost, longest survival
         iii. Fistula maturation often takes weeks or months to establish adequate blood flow.
      b. Arteriovenous graft
         i. Usually synthetic (polytetrafluoroethylene)
         ii. Often used in patients with vascular disease
      c. Catheters
         i. Commonly used if permanent access unavailable
         ii. Problems include high infection and thrombosis rates. Low blood flow leads to inadequate dialysis.
   2. Dialysis membranes
      a. Conventional: Not often used anymore. Small pores, smaller surface area
      b. High flux (large pores) and high efficiency (large surface area). Can remove drugs that were impermeable to standard membranes (vancomycin). Large amounts of fluid removed (ultrafiltrate)
   3. Adequacy
      a. Kt/V: Unitless parameter. K = clearance, t = time on dialysis, and V = volume of distribution of urea. KDOQI set a minimum of 1.2 (target Kt/V of 1.4).
      b. URR: Urea reduction ratio. URR = [(preBUN – postBUN)/preBUN] × 100%. Goal URR is greater than 65% (target URR of 70%).
   4. Common complications of HD
      a. Intradialytic
         i. Hypotension: Related primarily to fluid removal. Common in older adults and in people with diabetes mellitus
            (a) Acute treatment: Trendelenburg position, decrease ultrafiltration rate; administer saline boluses
            (b) Prevention: Accurately set "dry weight"; limit fluid gains between sessions; midodrine 2.5–10 mg orally before dialysis
            (c) Less well-studied agents include fludrocortisone, selective serotonin reuptake inhibitors
         ii. Cramps: Vitamin E 400 international units at bedtime
         iii. Nausea and vomiting
         iv. Headache, chest pain, or back pain

   b. Vascular access complications: Most common with catheters
      i. Infection: *Staphylococcus aureus* is the most common organism. Need to treat aggressively. May need to remove catheter
      ii. Thrombosis: Suspected with low blood flow. Oral antiplatelet agents for prevention not used because of lack of efficacy. Can treat with alteplase 2 mg or reteplase 0.4 unit per lumen; allow to dwell and try to aspirate after 30 minutes; may repeat dose if needed
5. Factors that affect the efficiency of HD
   a. Type of dialyzer used (changes in membrane surface area and pore size)
   b. Length of therapy
   c. Dialysis flow rate
   d. Blood flow rate

D. Continuous RRT for Critically Ill Patients with AKI
1. Continuous venovenous hemofiltration (CVVH): Removes fluid and solutes by convection rather than by diffusion
   a. Drug removal depends on ultrafiltrate production rate and protein binding of drug. Predict drug removal by the sieving coefficient (SC):

$$SC = \frac{\text{concentration of drug in ultrafiltrate}}{\text{concentration of drug in blood}}$$

   b. Requires replacement fluid because of high ultrafiltration rate
2. Continuous venovenous hemodialysis (CVVHD): Dialysate flows countercurrent to blood flow, and solute is removed by diffusion.
3. Continuous venovenous hemodiafiltration (CVVHDF): Ultrafiltration and dialysis; solute is removed by both convection and diffusion. Requires both replacement fluid and dialysate

E. Peritoneal Dialysis
1. Peritoneal dialysis membrane is 1–2 m^2 (approximates the body surface area) and consists of the vascular wall, the interstitium, the mesothelium, and the adjacent fluid films. 1.5–3 L of peritoneal dialysate fluid may be instilled in the peritoneum (fill) by a catheter, allowed to dwell for a specified time, and then drained.
2. Solutes and fluid diffuse across the peritoneal membrane.
3. Peritoneal dialysis is usually *not* used to treat AKI in adults.
4. Types of peritoneal dialysis
   a. Continuous ambulatory peritoneal dialysis: Classic. Requires mechanical process, which requires many manual exchanges throughout the day. Can disrupt daytime routine
   b. Automated peritoneal dialysis: Many variants exist, but continuous cycling peritoneal dialysis is the most common. Patient undergoes many exchanges during sleep by a cycling machine. May have one or two dwells during day. Minimizes potential contamination. Lowest incidence of peritonitis
5. Complications of peritoneal dialysis
   a. Peritonitis – Infection of the peritoneal cavity
      i. Patient technique and population variables influence the infection rate. Older adults or those with diabetes have a higher infection rate. Peritonitis is a main cause of failure of peritoneal dialysis.
      ii. Diagnosis: At least two of the following:
         (a) Clinical features consistent with peritonitis (i.e., abdominal pain and/or cloudy dialysis effluent)
         (b) Dialysis effluent WBC greater than 100/mm^3 or greater than 0.1×10^3 cells/m^3 (after a dwell time of at least 2 hours) with greater than 50% polymorphonuclear leukocytes

(c) Positive dialysis effluent culture (International Society for Peritoneal Dialysis [ISPD] guideline, 1C)

iii. Patients on peritoneal dialysis presenting with cloudy effluent can be presumed to have peritonitis and can be treated as such until diagnosis can be confirmed or excluded (ISPD guideline, 1C).

iv. Etiologic organisms: Most common gram-positive organisms include *Staphylococcus epidermis*, *S. aureus*, and streptococci. Most common gram-negative organisms include *Escherichia coli* and *Pseudomonas aeruginosa*.

v. Treatment based on ISPD guidelines

(a) Empiric treatment should cover gram-positive and gram-negative bacteria.

(b) Vancomycin or a first-generation cephalosporin is administered to cover gram-positive organisms, and a third-generation cephalosporin, an aminoglycoside, or aztreonam is added to cover gram-negative organisms. Intraperitoneal administration is preferred unless the patient has another systemic site of infection.

(c) Adjust as needed on the basis of culture and sensitivity.

b. Catheter exit-site infections

i. Recommended that daily topical application of antibiotic (mupirocin or gentamicin) cream or ointment be applied to catheter exit site for prophylaxis. (ISPD guideline, 1B)

ii. Prompt treatment of exit-site or catheter tunnel infection is recommended to reduce subsequent peritonitis risk (ISPD guideline, 1C).

c. Hyperglycemia

d. Fluid overload

e. Electrolyte abnormalities: Hypercalcemia, hypocalcemia

f. Malnutrition: Hypoalbuminemia

g. Hernia

Patient Case

Questions 16 and 17 pertain to the following case.

A 60-year-old patient on HD has had ESRD for 10 years. His HD access is a left arteriovenous fistula. He has a history of hypertension, coronary artery disease, mild CHF, type 2 diabetes, and a seizure disorder. Medications are as follows: epoetin alfa 14,000 units intravenously three times/week at dialysis, a renal multivitamin once daily, atorvastatin 20 mg/day, insulin, calcium acetate 2 tablets three times daily with meals, phenytoin 300 mg/day, and intravenous iron 100 mg/month. Laboratory values are as follows: Hgb 10.2 g/dL, iPTH 800 pg/mL, Na 140 mEq/L, K 4.9 mEq/L, SCr 7.0 mg/dL, calcium 9.5 mg/dL, albumin 2.5 g/dL, and phosphorus 7.8 mg/dL. Serum ferritin is 550 ng/mL, and TSAT is 32%. The red blood cell count indices are normal. His WBC is normal, and he is afebrile.

16. Which is most likely contributing to this patient's relative epoetin resistance?

A. Hyperparathyroidism.

B. Iron deficiency.

C. Phenytoin therapy.

D. Infection.

17. In addition to diet modification and emphasizing adherence, which is best for managing this patient's hyperparathyroidism?

A. Increase calcium acetate.

B. Change calcium acetate to sevelamer and add cinacalcet.

C. Hold calcium acetate and add intravenous vitamin D analog.

D. Add intravenous vitamin D analog.

V. MANAGING THE COMPLICATIONS OF CHRONIC KIDNEY DISEASE

A. Anemia

1. Several factors are responsible for anemia in CKD: Decreased erythropoietin production (most important), shorter life span of red blood cells, blood loss during dialysis, iron deficiency, anemia of chronic disease, and renal osteodystrophy
2. Prevalence: 26% of patients with a GFR greater than 60 mL/minute/1.73 m^2 have anemia, compared with 78% of patients with a GFR less than 15 mL/minute/1.73 m^2.
3. Signs and symptoms: Similar to those of anemia associated with other causes
4. Treatment: Treatment of anemia in CKD can decrease morbidity and mortality, reduce left ventricular hypertrophy, increase exercise tolerance, and increase quality of life.
5. Studies suggest that treatment with erythropoiesis-stimulating agents (ESAs) to high Hgb concentrations (greater than 13 g/dL) increases cardiovascular events. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), for example, failed to show a benefit in outcomes, but treatment with ESAs was associated with increased stroke (N Engl J Med 2009;361:2019-32). This supported earlier data from the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial (N Engl J Med 2006;355:2085-98) and the Cardiovascular Risk Reduction by Early Anemia Treatment with epoetin beta (CREATE) trial (N Engl J Med 2006;355:2071-84).
    a. Anemia workup: Initiate evaluation when CrCl is less than 60 mL/minute/1.73 m^2 *or* when Hgb is less than 13 g/dL (men) or less than 12 g/dL (women).
        i. Hgb and Hct monitoring recommendations (Table 9)

Table 9. Frequency of hemoglobin (Hgb) and Hematocrit (Hct) monitoring for patients at various stages of CKD

Stage of CKD	Frequency of Monitoring
3	At least annually
4 and 5 (non-dialysis)	At least twice per year
5 (dialysis)	At least every 3 mo

        ii. Mean corpuscular volume
        iii. Reticulocyte count
        iv. Iron studies
            (a) TSAT (serum iron/total iron-binding capacity × 100): Assesses available iron
            (b) Ferritin: Measures stored iron
        v. Serum vitamin B_{12} and folate concentrations
        vi. Stool guaiac

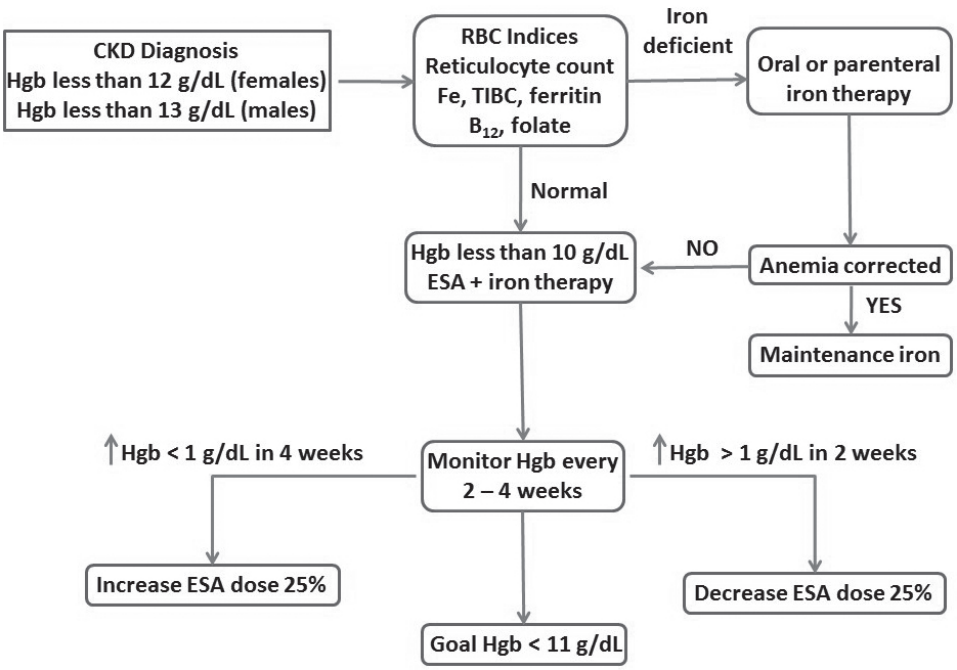


Figure 1. Management of anemia of CKD according to KDIGO and KDOQI guidelines.

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; Fe = iron; Hb = hemoglobin; RBC = red blood cell; TIBC = total iron-binding capacity.

b. ESAs
   i. Initiation
      (a) Patients with CKD (non-dialysis): Not to be initiated if Hgb is greater than 10 g/dL unless symptomatic. If Hgb is less than 10 g/dL, consider the rate of decline in Hgb and the need to reduce the likelihood of transfusion (particularly in patients who may receive a renal transplant).
      (b) Patients with CKD (dialysis): Initiate therapy for Hgb less than 10 g/dL (KDIGO guidelines recommend avoiding an Hgb decrease below 9 g/dL)
      (c) Use with caution, if at all, in patients with a history of stroke or cancer (evidence is stronger in non-dialysis patients than in dialysis patients).
      (d) Iron stores should be replaced before initiating ESAs.
      (e) Additional contraindications include uncontrolled hypertension and hypersensitivity reactions.
   ii. Maintenance of ESAs: Individualize dosing, and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions; adjust dosing as appropriate.
   iii. Epoetin alfa (Epogen, Procrit)
      (a) Same molecular structure as human erythropoietin (recombinant DNA technology)
      (b) Binds to and activates erythropoietin receptor
      (c) Administered subcutaneously or intravenously
      (d) Starting dose: 50–100 units/kg three times per week
      (e) Subcutaneous dosage requirement is typically 30% less than intravenous dosage requirement.
   iv. Darbepoetin alfa (Aranesp)
      (a) Molecular structure of human erythropoietin has been modified from 3 *N*-linked carbohydrate chains to 5 *N*-linked carbohydrate chains; increased duration of activity
      (b) The advantage is less-frequent dosing (e.g., once weekly, once every 2–3 weeks).

(c) Starting dose:
(1) Non-dialysis CKD: 0.45 mcg/kg once every 4 weeks
(2) Dialysis CKD: 0.45 mcg/kg once per week or 0.75 mcg/kg every 2 weeks
(d) Binds to and activates erythropoietin receptor
(e) May be administered subcutaneously or intravenously

v. Methoxy polyethylene glycol-epoetin beta (Mircera)
(a) Molecular structure of human erythropoietin has been modified through the formation of a chemical bond with methoxyl polyethylene glycol butanoic acid; increased duration of action
(b) Onset of Hgb increase occurs 7–15 days after initial dose.
(c) Less-frequent dosing; initial dose 0.6 mcg/kg body weight once every 2 weeks
(d) Once Hgb stabilizes, can double the dose and administer once monthly
(e) Binds to and activates erythropoietin receptor
(f) May be administered subcutaneously or intravenously

c. Therapy goals
i. Use the lowest possible dose of ESA to prevent blood transfusion.
ii. In non-dialysis patients with CKD, hold or reduce the dose when Hgb is greater than 10 g/dL.
iii. In dialysis patients, hold or reduce the dose when Hgb is greater than 11 g/dL (KDIGO suggests an upper limit of 11.5 g/dL).
iv. Do not exceed an Hgb greater than 13 g/dL.

d. ESA dose adjustment is based on Hgb response.
i. Adjustment parameters are similar for epoetin alfa and darbepoetin alfa.
ii. Maximal increase in Hgb is about 1 g/dL every 2–4 weeks.
iii. Dosages should not be titrated more often than every 4 weeks.
iv. In general, dose adjustments are made in 25% increments (i.e., dosages titrated or tapered by 25% according to current dose).

e. ESA monitoring (Table 10)
i. Hgb every 2–4 weeks during initiation phase. In maintenance phase of therapy, monitor Hgb at least monthly in dialysis patients and at least every 3 months in non-dialysis patients with CKD.
ii. Monitor blood pressure because it may rise (treat as necessary).
iii. Iron stores

Table 10. KDOQI and KDIGO Iron Status Goals

Laboratory Value	KDOQI	KDIGO
TSAT	> 20%	> 30%
Ferritin	> 100 ng/mL (non-dialysis CKD; PD) > 200 ng/mL (HD CKD)	> 500 ng/mL

HD = hemodialysis; PD = peritoneal dialysis.

Information from: KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target; Am J Kidney Dis 2007;50:471-530. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279.

f. Common causes of inadequate response to ESA therapy
i. Iron deficiency is the most common cause of erythropoietin resistance; however, increased use of intravenous iron products has reduced this problem.
ii. Infection and inflammation
iii. Other causes include chronic blood loss, hyperparathyroidism, aluminum toxicity, folate or vitamin B_{12} deficiency, malignancies, malnutrition, hemolysis, and vitamin C deficiency.

g. Iron therapy
   i. Oral iron is not recommended in patients with CKD on dialysis, but a 1- to 3-month trial may be done in predialysis patients with CKD requiring iron therapy.
   ii. Ferric citrate is FDA approved as a phosphate binder and may be useful for oral iron supplementation in patients with CKD not requiring dialysis.
   iii. Most patients with CKD who are receiving ESAs need parenteral iron therapy (increased requirements, decreased oral absorption).
   iv. For adult patients who undergo dialysis, an empiric cumulative or total dose of 1000 mg is usually given, and equations are rarely used.
   v. Monitor TSAT and ferritin as noted every 3 months.
   vi. Adverse effects
      (a) Anaphylactic-type reactions with iron dextran necessitate test dose. Hypersensitivity reaction may occur with all parenteral iron products.
      (b) Hypotension with administration of sodium ferric gluconate, iron sucrose, and ferumoxytol. Monitor during and up to 30 minutes after administration.
      (c) Hypertension. Transient increases in blood pressure occur with ferric carboxymaltose.
      (d) Bloodstream or other serious infections may be worsened by intravenous iron. In these circumstances, it may be appropriate to administer an ESA without repleting iron.
   vii. Seven commercial parenteral iron preparations are approved in the United States (Table 11).

Table 11. Parenteral Iron Therapy

Iron Product	Replacement Therapy (TSAT < 30% and ferritin < 500 ng/mL)	Maintenance Therapy (iron stores in goal)	Initial Test Dose
Iron dextran (high-molecular-weight iron dextran: Dexferrum) (low-molecular-weight iron dextran: INFeD)	IVP: 100 mg IV three times/wk during HD × 10 doses (1 g)	25–100 mg/wk IV × 10 wk	Yes; 25 mg one-time test dose
Sodium ferric gluconate complex (Ferrlecit and generic)	125 mg IV three times/wk during HD × 8 doses (1 g)	31.25–125 mg/wk IV × 10 wk	None needed
Iron sucrose (Venofer)	100 mg IV three times/wk during HD × 10 doses (1 g) For non-HD CKD, 200 mg IV × 5 doses	25–100 mg/wk IV × 10 wk	None needed
Ferumoxytol (Feraheme)	510 mg at up to 30 mg/s, followed by a second 510-mg IV dose 3–8 days later (all CKD)	N/A	None needed
Ferric carboxymaltose (Injectafer)	15 mg/kg IV up to 750 mg; may repeat after at least 7 days (maximum 1500 mg of elemental iron per two-dose course)	N/A	None needed

IV = intravenous(ly); IVP = intravenous push; IVPB = intravenous piggyback; N/A = not applicable; NS = normal saline solution.

B. CKD–Mineral and Bone Disorder (CKD-MBD)
   1. Pathophysiology: Calcium and phosphorus homeostasis is complex, involving the interplay of hormones affecting the bone, gastrointestinal (GI) tract, kidneys, and parathyroid gland. The process may begin as GFR decreases to less than 60 mL/minute/1.73 m^2. The consequences of CKD-MBD include renal osteodystrophy and vascular calcification. Factors contributing to CKD-MBD include the following:
      a. Hyperphosphatemia

b. Decreased production of 1,25-dihydroxyvitamin D_3
c. Reduced absorption of calcium in the gut
d. Decreased ionized (free) calcium concentrations
e. Direct stimulation of parathyroid hormone (PTH) secretion
f. Elevated PTH concentrations cause decreased reabsorption of phosphorus and increased reabsorption of calcium in the proximal tubule. This adaptive mechanism is lost as GFR decreases below 30 mL/minute/1.73 m^2. Important: Calcium is not well absorbed through the gut at this point, and calcium concentrations are maintained by increased bone resorption through elevated PTH. Unabated calcium loss from the bone results in renal osteodystrophy.

2. Prevalence
   a. Main cause of morbidity and mortality in patients undergoing dialysis
   b. Very common
3. Signs and symptoms
   a. Insidious onset: Patients may experience fatigue and musculoskeletal and GI pain; calcification may be visible on radiography; bone pain and fractures can occur if progression is left untreated.
   b. Laboratory abnormalities (Table 12)
      i. Phosphorus
      ii. Corrected calcium (measured calcium + 0.8[4 – serum albumin])
      iii. Intact parathyroid hormone (iPTH)
      iv. Alkaline phosphatase
      v. 25-hydroxyvitamin D

Table 12. KDIGO Guidelines for Frequency of Laboratory Monitoring in Stage 3–5 CKD[a]

	G3a–G3b CKD	G4 CKD	G5–G5D CKD
Calcium	Every 6–12 mo	Every 3–6 mo	Every 1–3 mo
Phosphorus	Every 6–12 mo	Every 3–6 mo	Every 1–3 mo
iPTH	Baseline[b]	Every 6–12 mo	Every 3–6 mo
Alkaline phosphatase	Baseline	Every 12 mo[c,d]	Every 12 mo[c,d]
25-hydroxyvitamin D	Baseline	Baseline	Baseline

[a]More frequent monitoring may be needed in patients receiving treatment.
[b]Subsequent frequency based on baseline concentration and CKD progression.
[c]May be monitored more often in the presence of elevated PTH.
[d]Repeat testing may be determined by baseline value and treatments.
iPTH = intact parathyroid hormone.

   c. Diagnostic testing
      i. Bone mineral density testing: Suggested for patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis if results will affect treatment decisions (KDIGO 2017, grade 2B)
      ii. Bone biopsy: Reasonable if knowledge of type of renal osteodystrophy will affect treatment decisions (KDIGO 2017, not graded)
4. Treatment should be based on serial assessments of phosphate, calcium, and PTH concentrations, considered together (KDIGO 2017, not graded).
   a. Therapy goals for patients with CKD G3a–G5D
      i. Suggest lowering phosphate concentrations toward normal range (KDIGO 2017, grade 2C)
      ii. In adults, suggest avoiding hypercalcemia (KDIGO 2017, grade 2C)
      iii. In patients with CKD G3a–G5 not on dialysis, evaluate for modifiable causes in patients with iPTH progressively rising or persistently above the upper normal limit (KDIGO 2017, grade 2C).

iv. In patients with CKD G5D, suggest maintaining iPTH concentrations 2–9 times the upper normal limits. Marked changes in either direction should prompt initiation of or change in therapy (KDIGO 2017, grade 2C).

b. Nondrug therapy
   i. Dietary phosphorus restriction 800–1000 mg/day in CKD category G3 or higher, alone or in combination with other treatments (KDIGO 2017, grade 2D). Reasonable to consider phosphate source in making dietary recommendations (KDIGO 2017, not graded)
   ii. Dialysis removes various amounts of phosphorus, depending on treatment modalities; however, by itself, dialysis is insufficient to maintain phosphorus balances in most patients.
   iii. Parathyroidectomy: Reserved for patients with unresponsive hyperparathyroidism

c. Phosphate binders: Take with meals to bind phosphorus in the gut; products from different groups may be used together for additive effect (Table 13).

Table 13. Phosphate Binders[a]

Product	Dosage Form	Typical Dose
Calcium carbonate	500, 1000, 1250 mg (40% elemental calcium)	1250 mg
Calcium acetate (PhosLo, Phoslyra)	667-mg capsule, tablet 667 mg/5 mL solution (25% elemental calcium)	2001 mg
Sevelamer hydrochloride (Renagel)	400-, 800-mg tablet	800–2400 mg
Sevelamer carbonate (Renvela)	800-mg tablet 0.8-g, 2.4-g packet	800–2400 mg
Lanthanum carbonate (Fosrenol)	500-, 750-, 1000-mg chewable tablet	250–500 mg
Sucroferric oxyhydroxide (Velphoro)	500-mg chewable tablet	500 mg
Aluminum hydroxide	320 mg/5 mL suspension	300–600 mg
Ferric citrate (Auryxia)	1 g (210 mg of ferric ion) tablet	2 g (420 mg of ferric ion)

[a]Typical dose is administered three times daily with meals.

   i. Decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (KDIGO 2017, not graded).
   ii. Calcium binders are often the initial phosphate binder for stage 3 and 4 CKD. Either calcium or nonionic binders can be the initial binder of choice in stage 5 CKD. No data analyses suggest that any phosphate binder is superior to another in clinical outcomes (mortality or hospitalization). In adult patients, suggest restricting the dose of calcium-based phosphate binders (KDIGO 2017, grade 2B)
   iii. Aluminum-containing phosphate binders (aluminum hydroxide, aluminum carbonate, and sucralfate) effectively lower phosphorus concentrations. In general, avoid long-term use (grade 1C). Not used as often because of aluminum toxicity (adynamic bone disease, encephalopathy, and erythropoietin resistance). Use should be limited to a single short-term (4 week) course.
   iv. Calcium-containing phosphate binders (calcium carbonate and calcium acetate)
      (a) Widely used phosphate binder. Carbonate salt is inexpensive.

(b) Carbonate is also used to treat hypocalcemia, which sometimes occurs in patients with CKD, and can decrease metabolic acidosis.
(c) Calcium acetate is a better binder than carbonate and contains less elemental calcium. Less calcium absorption
(d) Use may be limited by development of hypercalcemia; reduce dose or discontinue.
(e) Total elemental calcium is 2000 mg/day (1500-mg binder; 500-mg diet).

v. Sevelamer: A nonabsorbable phosphate binder
(a) Effectively binds dietary phosphorus
(b) As with calcium, considered primary therapy in stage 5 CKD. In particular, consider whether the patient has hypercalcemia or whether calcium intake exceeds the recommended dose with calcium-containing binders.
(c) Decreases low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol.
(d) Metabolic acidosis may worsen with sevelamer hydrochloride.

vi. Lanthanum carbonate
(a) As effective as aluminum in phosphate-binding capability. Not widely used, but indications similar to sevelamer
(b) Flavorless, chewable tablet
(c) Consider using if patient has hypercalcemia

vii. Ferric citrate: Iron-based phosphate binder
(a) 1 g of ferric citrate contains 210 mg of ferric ion.
(b) Initial dose: 2 tablets (420 mg ferric ion) three times daily with meals
(c) GI adverse effects and potential drug interactions similar to other oral iron preparations

viii. Sucroferric oxyhydroxide: Iron-based phosphate binder
(a) Initial dose: 500 mg three times daily with meals
(b) Tablet must be chewed.
(c) GI adverse effects and potential drug interactions similar to other oral iron preparations

d. Vitamin D and vitamin D analogs: Suppress PTH synthesis and reduce PTH concentrations; therapy is limited by resultant hypercalcemia
i. In adults with CKD G3a–G5, routine use of calcitriol and vitamin D analogs is not suggested (KDIGO 2017, grade 2C). Reasonable to reserve for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (not graded)
ii. Ergocalciferol (vitamin D_2): Inactive form of vitamin D. May be used in stage 3 or 4 CKD for patients with low serum 25-hydroxyvitamin D concentrations; repeat vitamin D concentrations after 6 months of therapy. Usually doses weekly or monthly (Table 14)
iii. Cholecalciferol (vitamin D_3): Inactive vitamin D. May be used as alternative to ergocalciferol. Usually dosed daily
iv. Calcifediol (25-hydroxyvitamin D_3): Undergoes 1-α-hydroxylation to calcitriol. May be used in patients with stage 3 or 4 CKD as alternative to ergocalciferol

Table 14. Ergocalciferol Repletion

Serum 25-Hydroxyvitamin D (ng/mL)	Assessment	Dosing Regimen
< 5	Severe deficiency	Weekly oral doses × 12 wk, then monthly *or* Single intramuscular dose
5–15	Mild deficiency	Weekly oral doses × 4 wk, then monthly
16–30	Insufficiency	Monthly oral doses

v. Calcitriol (Calcijex, Rocaltrol): The pharmacologically active form of 1,25-dihydroxyvitamin D_3 is FDA label approved for managing hypocalcemia and preventing and treating secondary hyperparathyroidism.
   (1) Oral and parenteral formulations
   (2) Does not require hepatic or renal activation
   (3) Low-dose daily oral therapy reduces hypocalcemia but does not significantly reduce PTH concentrations.
   (4) High incidence of hypercalcemia, limiting PTH suppression
   (5) Dose adjustment at 4-week intervals

vi. Paricalcitol (Zemplar): Vitamin D analog; FDA label approved for the treatment and prevention of secondary hyperparathyroidism
   (1) Parenteral and oral formulations
   (2) Does not require hepatic or renal activation
   (3) Lower incidence of hypercalcemia than with calcitriol (decreased mobilization of calcium from the bone and decreased absorption of calcium from the gut)

vii. Doxercalciferol (Hectorol): Vitamin D analog; FDA label approved for the treatment and prevention of secondary hyperparathyroidism
   (1) Parenteral and oral formulations
   (2) Prodrug; requires hepatic activation; may have more physiologic concentrations
   (3) Lower incidence of hypercalcemia than with calcitriol (decreased mobilization of calcium from the bone and decreased absorption of calcium from the gut)

e. Calcimimetics: Indicated for secondary hyperparathyroidism, especially in patients with high calcium and phosphate concentrations when vitamin D analogs cannot be used or cannot be increased

i. Cinacalcet hydrochloride (Sensipar): A calcimimetic that attaches to the calcium receptor on the parathyroid gland and increases the sensitivity of receptors to serum calcium concentrations, thus reducing PTH
   (1) Initial dose is 30 mg by mouth once daily, irrespective of PTH concentration.
   (2) Monitor serum calcium within 1 week after starting therapy or increasing the dose (risk of hypocalcemia is about 5%); do not initiate therapy if corrected serum calcium is less than 8.4 mg/dL.
   (3) Monitor iPTH (at least 12 hours post-dose) 1–4 weeks after initiating or adjusting therapy.
   (4) Can be used in patients irrespective of phosphate binder or vitamin D analog use
   (5) Caution in patients with seizure disorder (hypocalcemia may exacerbate)
   (6) Adverse effects are nausea (30%) and diarrhea (20%).
   (7) Cinacalcet inhibits cytochrome P450 (CYP) 2D6 metabolism, thereby inhibiting the metabolism of CYP2D6 substrates such that dose reductions in drugs with narrow therapeutic indices may be required (e.g., flecainide, tricyclic antidepressants, thioridazine).
   (8) Cinacalcet is metabolized primarily by CYP3A, so drugs that are potent inhibitors of CYP3A (ketoconazole) may increase cinacalcet concentrations by up to 2-fold.

ii. Etelcalcetide (Parsabiv): A synthetic peptide calcimimetic that activates the calcium-sensing receptor on the parathyroid gland, thus reducing PTH
   (1) Initial dose is 5 mg intravenously three times per week after HD.
   (2) Dose can be titrated in 2.5- to 5-mg increments at intervals of at least every 4 weeks.
   (3) If doses are missed for more than 2 weeks, reinitiate therapy at 5 mg three times per week.
   (4) Monitor corrected serum calcium before initiation and 1 week after initiation or dose adjustment. Once the dose is stabilized, monitor serum calcium every 4 weeks.
   (5) Monitor serum PTH before initiation and 4 weeks after initiation or dose adjustment.
   (6) Adverse effects include hypocalcemia, nausea, diarrhea, QT prolongation; may worsen heart failure

(7) Use with caution in patients with seizure disorder (hypocalcemia may exacerbate).
(8) Discontinue cinacalcet for at least 7 days before initiating etelcacetide, and discontinue etelcalcetide for 4 weeks before initiating cinacalcet..

f. Osteoporosis treatment
i. CKD category G1–G2 with osteoporosis and/or high risk of fracture, manage as for the general population (KDIGO 2017, grade 1A)
ii. CKD category G3a–G3b with normal PTH and osteoporosis and/or high risk of fracture, suggest treatment as for the general population (KDIGO 2017, grade 2B)
iii. CKD category G3a–G5D with biochemical abnormalities of CKD-MBD and low bone mineral density and/or fragility fractures, treatment choices consider the magnitude and reversibility of biochemical abnormalities and progression of CKD, with consideration of a bone biopsy (KDIGO 2017, grade 2D)

Patient Case

18. A 40-year-old patient on dialysis with a history of grand mal seizures takes phenytoin 300 mg/day. His albumin concentration is 3.0 g/dL. His total phenytoin concentration is 5.0 mcg/mL. Which best interprets the phenytoin concentrations?

A. Subtherapeutic; a dose increase is needed.
B. Therapeutic; no dosage adjustment is needed.
C. Toxic; a dose reduction is needed.
D. Not interpretable.

VI. DOSAGE ADJUSTMENTS IN KIDNEY DISEASE

A. The dosages of many drugs will require adjustment to prevent toxicity in patients with CKD. Adjustment strategies vary depending on whether the patient is receiving RRT and, if so, which type. The National Kidney Disease Education Program of the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases suggests that either eGFR or eCrCl be used for drug dosing. If eGFR is used in very large or small patients, it should be multiplied by the actual body surface area to obtain eGFR in milliliters per minute.

B. Pharmacokinetic Principles Guiding Therapy Adjustments
1. Absorption: Oral absorption can be decreased.
a. Nausea and vomiting
b. Increased gastric pH (uremia)
c. Edema
d. Physical binding of drugs to phosphate binders
2. Distribution
a. Changes in concentrations in highly water-soluble drugs occur as extracellular fluid status changes.
b. Acidic and neutral protein-bound drugs are displaced by toxin buildup. Other mechanisms include conformational changes of the plasma protein–binding site. Phenytoin is a classic example. The "normal" free fraction of phenytoin is 10%. Free fraction can be as high as 30% in patients with ESRD and hypoalbuminemia. Metabolic acidosis also increases dissociation of phenytoin from protein-binding sites.
i. Hypoalbuminemia correction:

$$\text{concentration adjusted} = \text{concentration measured}/[(0.2 \times \text{measured albumin}) + 0.1]$$

ii. Renal failure adjustment:

concentration adjusted = concentration measured/[(0.1 × measured albumin) + 0.1]

iii. Patients have lower total concentrations despite having adequate free concentrations (increased free fraction).
iv. Dosage adjustment of phenytoin not needed, just a different approach to evaluating concentrations

3. Metabolism: Variable changes can occur with uremia; metabolites can accumulate.
4. Excretion: Decreased

C. Pharmacodynamic changes can also occur (e.g., patients with CKD can be more sensitive to benzodiazepines).

D. General Recommendations
1. Patient history and clinical data
2. Estimate CrCl (Jelliffe or Brater equation in AKI; Cockcroft-Gault or MDRD study equations in stable kidney function).
3. Identify medications that require modification (Table 15).

Table 15. Dose Adjustments and Precautions in Decreased Kidney Function

Drug Class	Agents Requiring Dose Adjustment
Antibiotics	Almost all antibiotics require dosage adjustment (exceptions: ceftriaxone, clindamycin, linezolid, metronidazole, macrolides, nafcillin)
Anticoagulants	Enoxaparin, fondaparinux, apixaban, rivaroxaban, edoxaban, dabigatran
Cardiac medications	Atenolol, ACEIs, digoxin, nadolol, sotalol; avoid potassium-sparing diuretics if CrCl < 30 mL/min/1.73 m^2
Lipid-lowering therapy	Clofibrate, fenofibrate, statins (particularly rosuvastatin)
Narcotics	Codeine, avoid meperidine and morphine; other agents may also accumulate
Antipsychotic and antiepileptic agents	Chloral hydrate, gabapentin, lacosamide, levetiracetam, lithium, paroxetine, primidone, topiramate, trazodone, vigabatrin
Hypoglycemic agents	Acarbose, alogliptin, canagliflozin, chlorpropamide, dapagliflozin, exenatide, glyburide, glipizide, insulins, liraglutide, metformin, saxagliptin, sitagliptin
Antiretrovirals	Individualize therapy: Monitor $CD4^+$ counts, viral load, and adverse effects (agents requiring dose adjustment: lamivudine, adefovir, emtricitabine, didanosine, stavudine, tenofovir, and zidovudine)

4. Calculate drug doses individualized for the patient.
a. Published data
b. Rowland-Tozer estimate
i. Q = 1 − [Fe(1 − KF)]
ii. Q = kinetic parameter or drug dose adjustment factor
iii. Fe = fraction of drug excreted unchanged in the urine
iv. KF = ratio of patient's CrCl to normal (120 mL/minute/1.73 m^2)
5. Monitor patient (e.g., kidney function, clinical parameters) and drug concentration (if applicable).
6. Revise regimen as appropriate.

E. Drug Dosing in HD
   1. Dosing changes in patients with HD may be necessary because of accumulation caused by kidney failure *or* because the procedure may remove the drug from the circulation *or* because of pharmacodynamic effects (e.g., blood pressure medication reduction because of intradialytic hypotension).
   2. Drug-related factors affecting drug removal during dialysis
      a. Molecular weight: With high-flux membranes, larger molecules (e.g., vancomycin) can be removed compared with conventional filters.
      b. Water soluble: Insoluble drugs are not likely to be removed.
      c. Protein binding: Because albumin cannot pass through membranes, protein-bound drugs cannot pass through either.
      d. Volume of distribution: Drugs with a small volume of distribution (less than 1 L/kg) available in central circulation for removal. Large volumes of distribution cannot be removed (digoxin and tricyclic antidepressants), even if the protein binding is very low.
   3. Procedure-related factors affecting drug removal
      a. Type of dialyzer: High flux, widely used now
      b. Blood flow rate: Elevated rates increase delivery and maintain gradient across membrane.
      c. Duration of dialysis session
      d. Dialysate flow rate. High rates of flow increase removal by maintaining the gradient across membranes.

REFERENCES

Kidney Disease

1. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO Guidelines. Available at http://kdigo.org/home/guidelines/. Accessed August 18, 2020.
2. National Kidney Disease Education Program (NKDEP). Available at www.nkdep.nih.gov/. Accessed August 18, 2020.
3. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Available at https://www.kidney.org/professionals/guidelines. Accessed August 18, 2020.

Acute Kidney Injury

1. Bellomo R, Ronco C, Kellum JA, et al.; the ADQI Workgroup. Acute renal failure – definition, outcome measures, animal models, and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.
2. Kellum JA. Acute kidney injury. Crit Care Med 2008;36:S141-5.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.
4. Maker J, Roller L, Dager W. Acute kidney injury. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020:625-46.
5. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
6. Palevsky PM, Liu KD, Brophy PD, et al. KDOQI U.S. commentary on the 2012 KDIGO clinical practice guidelines for acute kidney injury. Am J Kidney Dis 2013;61:649-72.
7. Stamatakis MK. Acute kidney injury. In: Chisholm-Burns MA, Wells BG, Schwinghammer TL, et al., eds. Pharmacotherapy: Principles and Practice, 2nd ed. New York: McGraw-Hill, 2010:431-44.
8. Ympa YP, Sakr Y, Reinhart K, et al. Has mortality from acute kidney injury decreased? A systematic review of the literature. Am J Med 2005;118:827-32.

Glomerulonephritis

1. Beck L, Bomback AS, Choi MJ, et al. KDOQI U.S. commentary on the 2012 clinical practice guideline for glomerulonephritis. Am J Kidney Dis 2013;62:403-41.
2. Hogan JJ, Lau AH. Glomerular diseases. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020:715-38.
3. Kidney Disease: Improving Global Outcomes (KDIGO). Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2012;2:139-274.

Drug-Induced Kidney Damage

1. Nolin TD, Perazella MA. Drug-induced kidney disease. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020:697-714.
2. Schweiger MJ, Chambers CE, Davidson CJ, et al. Prevention of contrast induced nephropathy: recommendations for the high risk patient undergoing cardiovascular procedures. Catheter Cardiovasc Interv 2007;69:135-40.

Chronic Kidney Disease and Complications

1. American Diabetes Association (ADA). Cardiovascular disease and risk management: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(suppl 1):S111-S134.
2. American Diabetes Association (ADA). Microvascular complications and foot care: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(suppl 1):S135-S151.
3. American Diabetes Association (ADA). Summary of revisions: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(suppl 1):S4-S6.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285-350.
5. Hudson JQ, Wazny LD, Komenda P. Chronic kidney disease. In: DiPiro JT, Yee GC, Posey L, et al., eds.

Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020:647-76.

6. Inker LA, Astor BC, Fox CH, et al. KDOQI commentary on the 2012 clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014;63:713-35.
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.
8. Kramer HJ, Townsend RR, Griffin K, et al. KDOQI US commentary on the 2017 ACC/AHA hypertension guideline. Am J Kidney Dis 2019;73:437-58.
9. Levey AS, Coresh J. Chronic kidney disease. Lancet 2012;379:165-80.
10. National Kidney Foundation (NKF). KDOQI. Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(suppl 2):S1-180.
11. National Kidney Foundation (NKF). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(suppl 1):S1-266.
12. National Kidney Foundation (NKF). KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850-86.
13. National Kidney Foundation (NKF). KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004;43(suppl 5):S1.
14. Schonder KS. Chronic and end-stage renal disease. In: Chisholm-Burns MA, Wells BG, Schwinghammer TL, et al., eds. Pharmacotherapy: Principles and Practice, 2nd ed. New York: McGraw-Hill, 2010:445-78.
15. Taler SJ, Agarwal R, Bakris GL, et al. KDOQI U.S. commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. Am J Kidney Dis 2013;62:201-13.
16. Wanner C, Tonelli M; KDIGO Lipid Guideline Development Work Group Members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85:1303-9.

Anemia of Chronic Kidney Disease

1. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279-335. Available at https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf. Accessed September 1, 2020.
2. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI U.S. commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. Am J Kidney Dis 2013;62:849-59. Available at https://www.ajkd.org/action/showPdf?pii=S0272-6386%2813%2900978-5. Accessed September 1, 2020.
3. National Kidney Foundation (NKF). KDOQI clinical practice guidelines and recommendations for anemia of chronic kidney disease. Am J Kidney Dis 2006;47(suppl 3):S1-146. Available at http://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_anemia/index.htm. Accessed September 1, 2020.

Mineral and Bone Disorder

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney Int 2009;76(suppl 113):S1-130.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2017;7:1-59.
3. Uhlig K, Berns JS, Kestenbaum B, et al. KDOQI U.S. commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of CKD–mineral and bone disorder (CKD-MBD). Am J Kidney Dis 2010;55:773-99.

Renal Replacement Therapy

1. Ballinger AE, Palmer SC, Wiggins KJ, et al. Treatment for peritoneal dialysis-associated peritonitis. Cochrane Database Syst Rev 2014;4:CD005284.

2. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis: 2016 update on prevention and treatment. Perit Dial Int 2016;36:481-508.
3. O'Mara NB. Management of patients on dialysis. In: Murphy JE, Lee MW, eds. Pharmacotherapy Self-Assessment Program, 2014 Book 2. Chronic Illnesses. Lenexa, KS: American College of Clinical Pharmacy, 2014:203-7.
4. Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020:677-96.

Drug Therapy Adjustment in CKD

1. Battistella M, Nolin TD. Drug therapy individualization for patients with chronic kidney disease. In: DiPiro JT, Yee GC, Posey L, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 11th ed. New York: McGraw-Hill, 2020:739-54.
2. Kappel J, Calissi P. Nephrology: 3. Safe drug prescribing for patients with renal insufficiency. Can Med Assoc J 2002;166:473-7.
3. National Kidney Disease Education Program. Chronic Kidney Disease and Drug Dosing: Information for Providers. Revised April 2015. Available at https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-education-outreach/ckd-drug-dosing-providers. Accessed August 18, 2020.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient has AKI on the basis of either the increase in SCr of greater than 0.3 mg/dL in the past 24 hours or the decrease in urinary output of less than 0.5 mL/kg/hour (Answer D is incorrect). The patient's SCr concentration has increased by more than 1.9 times baseline, so it is not stage 1 (Answer A is incorrect). The SCr concentration has not increased more than 3 times baseline or achieved a concentration of greater than 4 mg/dL, and the patient has not required RRT, so it should not be classified as stage 3 (Answer C is incorrect). His urinary output of greater than 0.3 mL/kg/hour is also not consistent with stage 3 AKI. The increase in SCr of 2.0–2.9 times baseline and the patient's urinary output of less than 0.5 mL/kg/hour for more than 12 hours are both consistent with stage 2 AKI (Answer B is correct).

2. Answer: D

Fractional excretion of sodium can help distinguish prerenal AKI from intrinsic AKI. This calculation requires both urinary and serum concentrations of sodium and creatinine from a spot urine sample: FENa = [(urinary sodium/serum sodium)/(urinary Cr/SCr)] × 100 = [(45/140)/(20/2.1)] × 100 = 3.4% (Answer D is correct; Answers A–C are incorrect). This is greater than 2% and is consistent with decreased sodium reabsorption and increased renal sodium excretion.

3. Answer: B

This patient has AKI, probably because of ATN, a type of intrinsic renal failure (Answer B is correct). Hypotension despite rapid fluid resuscitation can cause ATN. The rapid rise in SCr, the BUN/SCr ratio of about 10:1, and the presence of muddy casts on urinalysis all suggest ATN. The FENa greater than 2% is also consistent with intrinsic AKI. There is no evidence of prerenal causes (volume depletion). The absence of an elevated BUN/SCr ratio greater than 20:1 and absence of low urinary sodium and low FENa are all suggest it is not prerenal AKI (Answer A is incorrect). Although lisinopril can cause a functional AKI, this usually occurs with initiation of therapy and presents similarly to prerenal AKI (Answer D is incorrect). Answer C is incorrect because there is no evidence of obstruction in this patient with urinary output present through the urinary catheter.

4. Answer: A

One strategy in managing AKI is to remove potentially nephrotoxic drugs, either direct toxins or medications that alter intrarenal hemodynamics. The following orders are common for patients in AKI: no ACEIs, ARBs, NSAIDs, or intravenous contrast. However, low-dose aspirin can be continued without adversely affecting kidney function (Answer D is incorrect). It is also important to remove (or reduce the dose of) agents that are cleared renally. Metformin, which accumulates in decreased kidney function, should temporarily be discontinued at this time because of an increased risk of lactic acidosis, not because of an adverse effect on kidney function (Answer C is incorrect). In this case, lisinopril is most likely to affect kidney function, so it should be discontinued (Answer A is correct). Unlike NSAIDs, acetaminophen does not interfere with prostaglandin synthesis peripherally; thus, it does not cause hemodynamically mediated AKI (Answer B is incorrect).

5. Answer: C

This patient presents with ATN, anuria, and volume overload. Although loop diuretics have not been shown to improve clinical outcomes in patients with AKI, they may increase urinary output, which will help with fluid and electrolyte balance. In addition, this patient is hypervolemic, so a trial of intravenous loop diuretics would be appropriate (Answer C is correct). Adding 0.9% sodium chloride (Answer A) would worsen fluid overload. Hydrochlorothiazide (Answer B) would not be appropriate because thiazide diuretics are unlikely to be effective with such poor kidney function. Fluid restriction (Answer D) may be necessary if furosemide fails to increase urinary output, but it would not be the first-line approach.

6. Answer: A

Intravenous 0.9% sodium chloride is considered the most effective hydration for preventing contrast-induced nephropathy (Answer A is correct). The other solutions, particularly oral, would not be appropriate because they are less effective at extracellular volume expansion (Answers B, C, and D are incorrect). Although not listed as a choice, intravenous sodium bicarbonate solutions have also been evaluated in this setting and offer no advantage over normal saline.

7. Answer: B

Contrast-associated nephropathy is associated with an acute rise in BUN and SCr within 24–48 hours, with a peak at 3–5 days. Monitoring of SCr at 24 hours (Answer B is correct) will help identify the development of contrast-associated nephropathy. In contrast, 6 hours is too early to detect a significant change (Answer A is incorrect), and waiting more than 48 hours would delay the detection of renal damage (Answers C and D are incorrect).

8. Answer: B

The patient's CKD should be classified as KDIGO category 3a (GFR 45–59 mL/minute/1.73 m^2) (Answer B is correct), which can be calculated by the MDRD formula or Cockcroft-Gault. The five categories range from mild kidney damage (G1) to kidney failure (G5). A patient's CKD would be classified as category G2 if the GFR were 60–89 mL/minute/1.73 m^2 (Answer A is incorrect), category G3b if the GFR were 30–44 mL/minute/1.73 m^2 (Answer C is incorrect), or category G4 if the GFR were 15–29 mL/minute/1.73 m^2 (Answer D is incorrect).

9. Answer: C

The KDIGO guideline also provides guidance on categorizing albuminuria according to the urinary ACR. This patient has category A3, or severely increased albuminuria, given the patient's ACR greater than 300 mg/g (Answer C is correct). Category A2 is moderately increased albuminuria with an ACR of 30–300 mg/g (Answer B is incorrect). Category A1 is an ACR less than 30 mg/g (Answer A is incorrect). Nephrotic-range proteinuria requires protein excretion exceeding 3 g/day (Answer D is incorrect).

10. Answer: C

Given the diagnosis of diabetes mellitus and the presence of severe albuminuria, this patient probably has diabetic nephropathy. Progression will be accelerated by smoking, poor diabetes control, and poor blood pressure control. In patients with diabetes, a target A1C of less than 7% is associated with a decrease in the rate of disease progression. Blood pressure control of less than 130/80 mm Hg in patients also decreases the progression of kidney disease. The standard of care in patients with diabetic nephropathy is ACEIs (evidence for reduced mortality and reduced progression of CKD) or ARBs (evidence for reduced progression but no mortality data), so enalapril (Answer C) is the best choice. A nondihydropyridine (Answer B) might be initiated in patients who cannot tolerate ACEI or ARB therapy, but this would not be a choice yet. Dihydropyridine therapy (Answer A) is not recommended in diabetic nephropathy because of conflicting literature on its efficacy. An increase in atenolol (Answer D) might control blood pressure, but inhibition of the renin-angiotensin system is still the best answer. In addition, a meta-analysis evaluating atenolol in patients with hypertension and diabetes mellitus found either no difference or worse outcomes.

11. Answer: A

The patient's blood pressure is not at goal (should be less than 130/80 mm Hg). To improve blood pressure control and increase the effect of the ACEI, chlorthalidone should be added (Answer A). Monitoring of SCr and serum potassium is appropriate in this patient. The SCr increase is less than 30%, so enalapril should be continued, making Answers B and C incorrect. Adding chlorthalidone will also counter the tendency for hyperkalemia. Answer D would likely lower blood pressure but would not be the preferred approach because renal protection would probably not be improved.

12. Answer: B

Calculation of the number needed to harm (NNH) is similar to calculation of the number needed to treat but is focused on a negative outcome. In this study, the risk of AKI was 11% in the monotherapy group and 18% in the combination therapy group, a difference of 7%. The NNH is calculated as 1/(absolute risk increase) = 1/(0.07) = 14.3. Hence, the best estimate is that one additional patient would develop AKI for about every 14 patients treated with combination therapy compared with ARB therapy alone (Answer B is correct; Answers A, C, and D are incorrect). When calculating the NNH, it is best to round the number down to the nearest whole number, in contrast to calculating the number needed to treat, when the number is rounded up.

13. Answer: D

A native arteriovenous fistula (Answer D) is the preferred access for chronic HD. If an arteriovenous fistula cannot be constructed, a synthetic arteriovenous graft (Answer C) is considered second line. A subclavian

catheter (Answer A) would be a poor choice because of the greater risk of infection and thrombosis and because of the poor blood flow obtained through a catheter. A Tenckhoff catheter (Answer B) is incorrect because this is a catheter for peritoneal dialysis.

14. Answer: D

The best-studied agent is midodrine, an α_1-agonist (Answer D). Levocarnitine (Answer A) has been tried, but data are limited on its benefit. Fludrocortisone (Answer C) is a synthetic mineralocorticoid that is used for hypotension in other situations; however, its primary mechanism is caused by sodium and water retention in the kidney; therefore, this drug is less likely to work. Sodium chloride tablets (Answer B) would not work acutely, and they should generally be avoided.

15. Answer: C

Empiric coverage for the treatment of peritoneal dialysis–related peritonitis should include activity against both gram-positive and gram-negative organisms (Answers B and D are incorrect). Intraperitoneal administration is preferred to intravenous administration. Cefazolin will provide activity against *Staphylococcus* unless an area has a high rate of methicillin-resistant organisms (Answer C). The choice of antibiotic for gram-negative coverage can include a third-generation cephalosporin with activity against *Pseudomonas* (e.g., ceftazidime, cefepime) (Answer C) or an aminoglycoside. Short-term use of an aminoglycoside should not adversely affect residual renal function. For patients with dialysis-related peritonitis, empiric anaerobic coverage is unnecessary (Answers A and B are incorrect).

16. Answer: A

Hyperparathyroidism is associated with epoetin resistance in patients on HD (Answer A). Although iron deficiency is the most common cause of epoetin deficiency, this patient's laboratory results do not indicate iron deficiency (Answer B) because TSAT is greater than 30% and serum ferritin is greater than 500 ng/mL. Phenytoin therapy (Answer C) has been associated with anemia in other patient populations but not in patients on HD. Infection (Answer D) and inflammation are very common causes of epoetin deficiency in patients on HD, but nothing in this patient's presentation suggests an infectious or inflammatory process.

17. Answer: B

This patient needs treatment for his elevated iPTH (800 pg/mL), which places him at high risk of renal osteodystrophy and vascular calcification. He has high serum phosphorus, and although the measured serum calcium concentration is normal, his corrected calcium concentration is elevated, given the presence of hypoalbuminemia (corrected calcium is 10.7 mg/dL). Current phosphate binder therapy is contributing to calcium exposure; therefore, calcium acetate should be discontinued and sevelamer initiated; also, cinacalcet should be added, which will lower iPTH and, potentially, serum calcium (Answer B is correct). Answer A is incorrect because increasing the calcium acetate may worsen the hypercalcemia. Answer C is incorrect for two reasons. First, the patient needs some type of phosphate binder; second, intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated iPTH in the presence of hyperphosphatemia. Answer D is incorrect because intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated iPTH in the presence of hyperphosphatemia. Because this patient also has a seizure disorder, close monitoring of serum calcium concentrations is recommended with the introduction of cinacalcet and discontinuation of calcium acetate. Significant reductions in serum calcium can lower the seizure threshold and potentially worsen seizures.

18. Answer: B

The presence of kidney failure and low serum albumin concentrations results in an increased free fraction of phenytoin, so the measured phenytoin concentration cannot be assumed to be subtherapeutic because it is less than 10 mcg/mL (Answer A is incorrect). However, the concentration can be interpreted with proper adjustment for the presence of renal failure and the patient's measured serum albumin (Answer D is incorrect). Use of the formula that adjusts for hypoalbuminemia in a patient with normal renal function would indicate the concentration is subtherapeutic, but this is not appropriate for a patient on dialysis (Answer A is incorrect). Using the correction equation for a patient with renal failure (adjusted phenytoin concentration = concentration measured/[(0.1 × albumin) + 0.1] = (5.0 mcg/mL)/[(0.1 × 3.0) + 0.1] = (5.0)/(0.4) = 12. 5 mcg/mL) gives a corrected phenytoin concentration within the therapeutic range (Answer B is correct; Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

Initial treatment of AKI requires identifying and reversing (if possible) the insult to the kidney. This patient's symptoms and presentation are consistent with prerenal azotemia because of volume depletion, so fluid administration would be the best choice (Answer C is correct). The patient has no suggestion of obstruction (e.g., distended abdomen, history of benign prostatic hypertrophy) (Answer B is incorrect). Diuretic administration would be inappropriate because it would worsen his volume depletion and probably further impair his kidney function (Answer A is incorrect). Fluid management is critical to managing AKI, necessitating a careful patient assessment. Although his glucose concentration is elevated, insulin is not necessary at this time (Answer D is incorrect).

2. Answer: C

The patient has intrinsic AKI (i.e., ATN). Aminoglycosides can cause direct damage to the tubules. In ATN, the BUN/SCr ratio would be normal (10–15:1), whereas an elevated BUN/SCr ratio (greater than 20:1) reflecting hypovolemia is common in prerenal azotemia (Answer A is incorrect). Urinary sodium of less than 20 mEq/L is also a marker of hypovolemia and would be consistent with prerenal azotemia AKI (Answer D is incorrect). Fractional excretion of sodium also distinguishes prerenal and intrinsic renal damage. A low FENa (less than 1%) in an oliguric patient suggests that tubular function is still intact, whereas a FENa greater than 2% is common in intrinsic renal failure (Answer C is correct). Cellular debris is often present in intrinsic renal failure because of renal tubular cell death or damage, whereas a normal urinalysis would be more consistent with prerenal AKI (Answer B is incorrect).

3. Answer: B

Information regarding the fraction of drug excreted in the urine (Fe) can help determine the proper dose of a drug when specific dosing guidelines are not available. The Rowland-Tozer equation can determine the percentage of the usual dose to give a patient with known kidney disease (Q), considering the ratio of the patient's renal function to normal (KF). For a patient with an estimated CrCl of 25 mL/minute/1.73 m^2, $Q = 1 - [Fe(1 - KF)] = 1 - [0.4(1 - 25/120)] = 1 - 0.32 = 0.68$, or 68% of the usual dose. If the usual dose is 600 mg, the adjusted dose would be 410 mg (600 mg × 0.68). Thus, the patient should receive 4.1 mL of the 100-mg/mL preparation (410 mg/100 mg/mL) (Answer B is correct; Answers A, C, and D are incorrect).

4. Answer: A

This patient is likely producing less creatinine, given his cancer, malnutrition, and associated decrease in muscle mass. Because his actual body weight is less than his ideal body weight, it is a better indicator of creatinine production; thus, it should be used in the Cockcroft-Gault formula (Answers C and D are incorrect). Although there is concern about the low SCr concentration in patients with malnutrition, measured SCr for use in the Cockcroft-Gault formula provides a better estimate of renal function than rounding the value to 1 mg/dL (Answers B and D are incorrect). Answer A is correct because it incorporates actual body weight and the measured SCr concentration.

5. Answer: C

This patient's Hgb is not at goal (greater than 10 g/dL), so maintaining the current regimen would not be appropriate (Answer D is incorrect). Iron studies show the patient is iron deficient, with TSAT less than 30% and ferritin less than 500 ng/mL (Answer A is incorrect). Increasing the epoetin dose would not increase red blood cell production in the absence of adequate iron. Although a trial of oral iron might be indicated in non–dialysis patients with CKD, patients on HD should be given intravenous iron as first line (Answer B is incorrect; Answer C is correct).

6. Answer: B

The presence of hypotension despite adequate hydration, a normal BUN/SCr ratio (10–15:1), urinary osmolality, and presence of urinary casts all point to ATN (Answer B is correct). Prerenal AKI is unlikely, considering adequate hydration, high urinary sodium (greater than 40 mEq/L), and lack of high urinary osmolality (Answer A is incorrect). Functional AKI would look similar to prerenal AKI on urinalysis with low urinary sodium and no tubular casts (Answer D is incorrect). Classically, AIN would present with eosinophils in the urine (Answer C is incorrect).

7. Answer: B

Hemoglobin represents continuous data. Because each treatment is administered to a separate group of patients, the data are not paired (i.e., they are unpaired) (Answer A is incorrect). Assuming the data are normally distributed, continuous unpaired data should be evaluated using a t-test (Answer B is correct). Analysis of variance can be used for continuous data, but only when three groups of data are compared (Answer C is incorrect). A chi-square test is used for nominal data (Answer D is incorrect).

8. Answer: D

A cost-utility analysis is an extension of the cost-effectiveness analysis in which the outcomes measured are lives saved, adjusted for changes in quality of life, measured as quality-adjusted life-years (Answer D is correct). A cost-minimization study compares the costs and consequences of two or more interventions that have equivalent outcomes, so the primary focus is on cost (Answer A is incorrect). A cost-effectiveness analysis compares costs and consequences to determine which treatment can achieve the best outcomes at the lowest cost (Answer B is incorrect). A cost-benefit analysis measures costs and consequences in monetary terms; this analysis may be useful to compare costs with unrelated outcomes (Answer C is incorrect).

9. Answer: C

Calculating the FENa helps assess AKI to help differentiate prerenal from ATN: FENa = [(urinary sodium)/(serum sodium)]/[(urinary creatinine)/(SCr)] × 100 = [(24 mEq/L)/(134 mEq/L)]/[(14.3 mg/dL)/(1.8 mg/dL)] × 100 = 2.3% (Answer C is correct). This FENa greater than 2% would be most consistent with ATN (Answers A, B, and D are incorrect).

10. Answer: B

The KDIGO guidelines provide recommendations for blood pressure goals for patients with CKD according to the severity of proteinuria. This patient is considered to have normal to mildly elevated albuminuria, with an ACR less than 30 mg/g. Patients with albuminuria in this category (A1) should have a goal blood pressure of less than 140/90 mm Hg (Answer B is correct). A goal blood pressure of less than 130/80 mm Hg would be desired for a patient with moderate to severe (category A2) albuminuria (Answer A is incorrect). Answer C is incorrect because the diastolic blood pressure goal is too low (80 mm Hg). Answer D is incorrect because the systolic blood pressure goal is too low (130 mm Hg).

11. Answer: D

This patient whose eGFR is 55 mL/minute/1.73 m^2 would be classified as having stage 3 CKD because his eGFR is less than 60 mL/minute/1.73 m^2. He does not currently have anemia because his Hgb concentration is greater than 13 g/dL. Therefore, Hgb should be monitored according to his CKD stage. For stage 3 CKD, monitoring is recommended at least every 12 months (Answer D is correct). For patients with stage 4 and stage 5 CKD who are not yet receiving dialysis, monitoring should occur at least every 6 months (Answer C is incorrect). Monitoring should occur at least every 3 months once patients in stage 5 CKD are receiving dialysis (Answer B is incorrect). Monthly monitoring is never recommended for a patient who is not currently anemic (Answer A is incorrect).

12. Answer: B

Many factors can contribute to the development of CKD-MBD, including hyperphosphatemia, hypocalcemia, decreased vitamin D and decreased production of active 1,25-dihydroxyvitamin D, and hyperparathyroidism. Although this patient's PTH concentration is elevated, it may be related to hyperphosphatemia. Therefore, the first approach would be to administer a phosphate binder such as calcium acetate to decrease his serum phosphate concentrations. A calcium-containing phosphate binder such as calcium acetate is acceptable with a corrected serum calcium concentration is the low-normal range [measured Ca + (0.8)(4 – serum albumin) = 8.6 mg/dL + (0.8)(3.5 – 3.0) = 8.6 + 0.4 = 9.0 mg/dL] (Answer B is correct). Ergocalciferol is not necessary in this patient because the 25-hydroxyvitamin D concentration is greater than 30 ng/mL, indicating adequate intake (Answer A is incorrect). The 2017 KDIGO CKD-MBD guidelines suggest that calcitriol should not be routinely used in G3–G5 CKD, but in G4–G5 CKD for patients with severe and progressive hyperparathyroidism (Answer C is incorrect). Cinacalcet is reserved for patients with hyperparathyroidism despite normalization of phosphate when hypercalcemia is present (Answer D is incorrect).

Pulmonary Disorders and Adult Immunizations

Emily M. Scopelliti, Pharm.D., BCPS

Thomas Jefferson University, Jefferson College of Pharmacy
Philadelphia, Pennsylvania

Pulmonary Disorders and Adult Immunizations

Emily M. Scopelliti, Pharm.D., BCPS

Thomas Jefferson University, Jefferson College of Pharmacy
Philadelphia, Pennsylvania

Learning Objectives

1. Design a patient-centered pharmacotherapy plan for initial treatment of asthma and chronic obstructive pulmonary disease according to evidence-based guidelines.
2. Assess the severity of a patient's asthma and chronic obstructive pulmonary disease on the basis of clinical presentation.
3. Adjust a patient's medication therapy for asthma and chronic obstructive pulmonary disease on the basis of symptom severity and clinical presentation.
4. Determine appropriate immunizations for an adult on the basis of patient-specific considerations, including age, medical conditions, contraindications, and immunization status.

Abbreviations in This Chapter

ACO	Asthma-COPD overlap
CAT	COPD Assessment Test
CCQ	COPD Control Questionnaire
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
DPI	Dry powder inhaler
ED	Emergency department
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Institute for Obstructive Lung Disease
HPV	Human papillomavirus
ICS	Inhaled corticosteroid
IL-5	Interleukin-5
LA	Long-acting
LABA	Long-acting β_2-agonist
LAMA	Long-acting anticholinergic/muscarinic antagonist
LTM	Leukotriene modifier
MDI	Metered-dose inhaler
MenACWY	Serogroups A, C, W, and Y meningococcal vaccine
MenB	Serogroup B meningococcal vaccine
mMRC	Modified Medical Research Council
OCS	Oral corticosteroid
PDE-4	Phosphodiesterase type 4
PEFR	Peak expiratory flow rate
PPSV23	23-valent pneumococcal polysaccharide vaccine; Pneumovax
SA	Short-acting
SABA	Short-acting β_2-agonist
SAMA	Short-acting anticholinergic/muscarinic antagonist
Sao_2	Oxygen to achieve oxygen saturation
Td	Tetanus and diphtheria vaccine
Tdap	Tetanus, diphtheria, and pertussis vaccine

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.

A 20-year-old woman presents to the clinic with an asthma exacerbation. She states that she has been using her boyfriend's albuterol inhaler on a regular basis for the past 2 years. During the past few months, she has been using the inhaler on a daily basis and sometimes at night.

1. Which description best classifies her asthma severity?
   A. Mild intermittent.
   B. Mild persistent.
   C. Moderate persistent.
   D. Severe persistent.

2. Which is the best asthma maintenance therapy for this patient?
   A. Fluticasone low dose.
   B. Montelukast.
   C. Fluticasone low dose plus salmeterol.
   D. Fluticasone high dose.

3. Which type of data best classifies the number of times a low-dose inhaled corticosteroid/formoterol inhaler is used in 1 month?
   A. Nominal.
   B. Ordinal.
   C. Interval.
   D. Ratio.

4. You are designing a study in which you will compare the percentages of patients with an asthma-related hospitalization receiving fluticasone/salmeterol and those receiving fluticasone alone. Which statistical test is best for analyzing this comparison?
   A. Analysis of variance (ANOVA).
   B. Chi-square.
   C. Mann-Whitney *U* test.
   D. Unpaired t-test.

5. A 22-year-old woman with asthma is taking an albuterol metered-dose inhaler (MDI) 2 puffs as needed and fluticasone (Flovent) 110 mcg/puff MDI 2 puffs twice daily. She received the influenza vaccine during last year's influenza season, and her last tetanus vaccine (tetanus, diphtheria, and pertussis [Tdap]) was at age 17; there is no documentation of her having received a pneumococcal vaccine. Which is the best vaccine for her to receive at her next family medicine clinic appointment, scheduled for July?
   A. Influenza.
   B. Pneumococcal.
   C. Tetanus and diphtheria (Td).
   D. Herpes zoster.

6. A 60-year-old man with COPD has been using albuterol 2 puffs four times per day as needed. His symptoms have worsened during the past year, and he now has persistent symptoms and shortness of breath, even while walking around his single-floor house. His Modified Medical Research Council (mMRC) score is 2. His spirometry reveals a forced expiratory volume in 1 second (FEV_1) of 70% of predicted and an FEV_1/forced vital capacity (FEV_1/FVC) of 60% of predicted. He has had no previous COPD exacerbations. Which medication is best to initiate?
   A. Inhaled fluticasone.
   B. Inhaled tiotropium.
   C. Inhaled fluticasone/salmeterol.
   D. Oral roflumilast.

7. A 75-year-old woman with a 50 pack-year history of tobacco use presents to her primary care physician with a complaint of worsening shortness of breath over the past 6 months. She has no documented history of asthma or COPD. Which symptom is most consistent with the diagnosis of COPD?
   A. Dyspnea that is progressive, persistent, and worse with exertion.
   B. FEV_1/FVC greater than 70% of predicted.
   C. Chronic cough present only at night.
   D. COPD Assessment Test (CAT) score of 5.

8. A 68-year-old man was given a diagnosis of COPD 1 year ago, and his symptoms have been managed with an albuterol inhaler as needed since. Recent spirometry revealed an FEV_1/FVC less than 70% and FEV_1 of 65%. Last week, he was discharged from the hospital after his first COPD exacerbation. His current mMRC score is 1. Which listing of COPD patient group and corresponding treatment is most appropriate for this patient?
   A. Group A: Continue albuterol as needed.
   B. Group B: Continue albuterol as needed.
   C. Group C: Continue albuterol as needed; add tiotropium daily.
   D. Group D: Continue albuterol as needed; add fluticasone furoate/vilanterol daily.

9. A 32-year-old woman, 30 weeks pregnant, is seen for a routine prenatal check today (October). This is her second pregnancy in 3 years. During her first pregnancy, she received Tdap at 36 weeks' gestation; her last tetanus booster was at age 21. She received all of her routine childhood immunizations. Which immunizations would be best for her today?
   A. Td.
   B. Td and influenza.
   C. Tdap.
   D. Tdap and influenza.

10. A 21-year-old man is seen for his annual wellness exam in July. He received an influenza vaccine last October but states that it was his first immunization in about 10 years. He works full-time at an office job that requires no travel. Which vaccines would be best for him today?

A. Tdap, human papillomavirus (HPV).
B. Tdap, influenza, meningococcal polysaccharide.
C. Td, meningococcal polysaccharide, HPV.
D. Td, influenza.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Specific Pharmacotherapy
    a. Task 1; Knowledge 1–8, 10–15, 17
    b. Task 3; Knowledge 1–4
    c. Task 4; Knowledge 1–7
    d. Task 5; Knowledge 1-4
2. Domain 2: Drug Information and Evidence-Based Medicine
    a. Task 2; Knowledge 1, 2, 5, 6
3. Domain 3: System-Based Standards and Population-Based Pharmacotherapy
    a. Task 1; Knowledge 3
    b. Task 4; Knowledge 1
    c. Task 6; Knowledge 1–3

I. ASTHMA

Guidelines:

National Institutes of Health (NIH) National Heart Lung and Blood Institute (NHLBI). National Asthma Education and Prevention Program Guidelines (NAEPP). NAEPP Expert Panel Report 3. NIH Publication 08-5846. July 2007. Available at https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed August 23, 2020.

Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2020. Available at www.ginasthma.org/. Accessed August 23, 2020.

A. Definition: Asthma is a chronic inflammatory disorder of the airways causing recurrent episodes of wheezing, breathlessness, cough, and chest tightness, particularly at night or early in the morning. During episodes, there is variable airway obstruction, often reversible spontaneously or with treatment. There is also increased bronchial hyperresponsiveness to a variety of stimuli.

B. Diagnosis
   1. Episodic symptoms of airflow obstruction are present.
   2. Airway obstruction is reversible (FEV_1 improves by 12% or more after short-acting β2-agonists [SABAs]).
   3. Alternative diagnoses are excluded. Asthma versus COPD:
      a. Cough is usually nonproductive with asthma and productive with COPD.
      b. FEV_1 is reversible with asthma but irreversible with COPD.
      c. Cough is worse at night and early in the morning with asthma; it occurs throughout the day with COPD.
      d. Asthma is often related to allergies and environmental triggers; patients with COPD have a common history of smoking or exposure to other irritants.
      e. Asthma can be reversible; lung damage from COPD is irreversible.
   4. Asthma-COPD overlap (ACO)
      a. No single definition of ACO is well defined or commonly accepted.
      b. The term ACO is no longer preferred because asthma should not be viewed as a single disease; rather, it is a clinical phenotype with shared clinical features of two separate diseases.
      c. Characterized by persistent airflow limitation and features associated with both asthma and COPD
      d. Table 1 includes clinical features of patients with asthma and/or COPD with recommended initial treatments.
   5. Exercise-induced bronchospasm
      a. It presents with cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during or after exercise.
      b. Diagnosis is made with an exercise challenge in which a 15% decrease in FEV_1 or peak expiratory flow occurs before and after exercise, measured at 5-minute intervals for 20–30 minutes.

Table 1. Initial Treatment Approach in Patients with Asthma and/or COPD

Adults with Chronic Respiratory Symptoms (dyspnea, cough, chest tightness, and wheeze)			
	Treat as asthma if several of the following features are present:	**Treat as asthma** if features of both asthma and COPD are present:	**Treat as COPD** if several of the following features are present:
History	– Symptoms vary over time and in intensity – Triggers: Laughing, exercise, allergens, seasonal – Onset < 40 yr of age – Symptoms improve with bronchodilators or ICS within days to weeks	– Symptoms intermittent or episodic – Onset before or after age 40 – May have history of smoking and/or toxic exposures, low birth weight, or respiratory illness (e.g., tuberculosis) – Any asthma features listed in the column to the left (e.g., triggers, symptom improvement with bronchodilators or ICS, current asthma diagnosis or previous diagnosis as a child)	– Persistent dyspnea on most days – Onset > 40 yr of age – Limitation of physical activity – May have been preceded by cough or sputum – Bronchodilator provides limited relief – History of smoking and/or toxic exposures, low birth weight, or respiratory illness (e.g., tuberculosis) – No past/current asthma diagnosis
Lung function	– Variable expiratory airflow limitation – Persistent airflow limitation may be present	– Persistent expiratory airflow limitation – With or without bronchodilator reversibility	– Persistent expiratory airflow limitation – With or without bronchodilator reversibility
Initial treatment	– ICS-containing treatment essential – Do not give LABA and/or LAMA without ICS – Avoid maintenance OCS	– ICS-containing treatment essential – Additional COPD treatments per GOLD recommendations – Do not give LABA and/or LAMA without ICS – Avoid maintenance OCS	– Treat as COPD per GOLD recommendations – Avoid high-dose ICS, avoid maintenance OCS
Reevaluate in 2–3 mo. Specialist referral if diagnosis remains uncertain or treatment response is inadequate			

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist; OCS = oral corticosteroid.

Information from: Global Initiative for Asthma (GINA). 2020 GINA Report. Global Strategy for Asthma Management and Prevention. Available at https://ginasthma.org/gina-reports/. Accessed December 21, 2020.

Table 2. Interpreting Spirometry

Component	What It Measures	Normal Values
FEV_1	Volume of air exhaled forcefully in the first second of maximal expiration	Normal is ≥ 80% In asthma, reversibility is shown by an increase in FEV_1 or FVC ≥ 12% and > 200 mL after SABA
FVC	Maximum volume of air that can be exhaled after full inspiration	Reported in liters and percentage predicted Adults with normal lung function can empty 80% of air in < 6 seconds
FEV_1/FVC ratio	Percentage of lung capacity able to be expelled in one second	Normal: Within 5% of predicted range, which varies with age; usually 75%–80% in adults Decreased in obstructive disease (asthma, COPD) (< 70%)

SABA = short-acting β-agonist.

C. Classification of Asthma Severity and Control (Tables 3 and 4)
   1. GINA 2020 assessment of asthma in adults
      a. Assess symptom control from frequency of day- and nighttime symptoms, reliever inhaler use, and activity limitation.
      b. Consider symptom tools such as the Asthma Control Test and Asthma Control Questionnaire.
      c. Assess risk of future exacerbations, even when control is good.
   2. GINA 2020 assessment of asthma control in children 6–11 years old
      a. Symptom control on the basis of symptoms, limitation of activities (daily activities, sports, play, social life, school attendance), and use of rescue medication
      b. Parents may report irritability, tiredness, and mood changes when asthma is uncontrolled.
      c. Asthma control scores for children include Childhood Asthma Control Test, Asthma Control Questionnaire, and Test for Respiratory and Asthma Control in Kids.
   3. Categories of asthma severity
      a. Mild: Well controlled on step 1 or step 2 treatment
      b. Moderate: Well controlled on step 3 treatment
      c. Severe: Requires step 4 or step 5 treatment to prevent it from being "uncontrolled" or if it remains uncontrolled despite step 4 or 5 treatment

Table 3. Classification of Asthma Severity in Adults and Children According to NAEPP EPR3 (2012)[a]

Components	Age Group (yr)	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Frequency of symptoms	All ages	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Throughout the day
Nighttime awakening	≥ 12	≤ 2 times/mo	3 or 4 times/mo	More than once weekly but not nightly	Often 7 times/wk
	5–11				
	0–4	0	1 or 2 times/mo	3 or 4 times/mo	More than once weekly
SABA; used for symptom control	All ages	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Several times a day
Interference with normal activity	All ages	None	Minor limitation	Some limitations	Extremely limited
FEV_1/FVC[b]	≥ 12	Normal	Normal	Reduced 5%	Reduced > 5%
	5–11	> 85%	> 80%	75%–80%	< 75%
	0–4	N/A			
FEV_1 (% of normal)	≥ 12	> 80% (normal)	> 80% (normal)	> 60% to < 80%	< 60%
	5–11				
	0–4	N/A			
Exacerbations requiring oral steroids	≥ 12	0 or 1/yr	≥2/yr[c]		
	5–11				
	0–4	0 or 1/yr	≥2 in 6 mo or ≥4 wheezing episodes lasting > 1 day per year[d]		

Table 3. Classification of Asthma Severity in Adults and Children According to NAEPP EPR3 (2012)[a] *(Cont'd)*

Components	Age Group (yr)	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Recommended step for initiating treatment (see Table 5)	≥ 12	Step 1	Step 2	Step 3[e] and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	5–11				Step 3[d] or 4 and consider short course of oral steroids
	0–4				Step 3 and consider short course of oral steroids

[a]The patient is classified according to the sign or symptom that is in the most severe category.

[b]Normal FEV_1/FVC: 8–19 yr old, 85%; 20–39 yr old, 80%; 40–59 yr old, 75%; 60–80 yr old, 70%.

[c]Considered the same as in patients who have persistent asthma, even without impairment levels consistent with persistent asthma.

[d]Episodes lasting > 1 day and risk factors for persistent asthma.

[e]For ages 5–11, initial step 3 therapy should be medium-dose ICS.

N/A = not applicable.

Adapted from: NIH Asthma Guidelines. National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. Available at https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed August 23, 2020.

Table 4. Assessing Asthma Control in Adults and Children ≥ 6 Yr

In the past 4 wk, has the patient had:			Well Controlled	Partly Controlled	Uncontrolled
Daytime asthma symptoms more than twice/week?	Yes	No	None of these	1 or 2 of these	3 or 4 of these
Any night waking because of asthma?	Yes	No			
SABA needed for symptoms more than twice/week?	Yes	No			
Any activity limitation because of asthma?	Yes	No			

SABA = short-acting β_2-agonist.

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2020. Available at www.ginasthma.org/. Accessed August 23, 2020.

D. Treatment Goals
   1. Minimal or no chronic symptoms day or night
   2. Minimal or no exacerbations
   3. No limitations on activities, no school or work missed
   4. Maintenance of (near) normal pulmonary function
   5. Minimal use of SABAs
   6. Minimal or no adverse effects from medications

E. Risk Factors for Poor Outcomes
   1. Uncontrolled asthma symptoms
   2. Medication factors: No ICS, poor adherence, incorrect technique, SABA use greater than 1 x 200 dose canister/month

3. Comorbid conditions: Obesity, gastroesophageal reflux disease, anxiety, depression, pregnancy
4. Environmental exposure: Smoking, allergens, air pollution
5. Lung function: FEV_1 less than 60% predicted, higher degree of reversibility
6. Fractional exhaled nitric oxide (FeNO) in allergic adults taking ICSs

F. Treatment Guidelines (Table 5)

Table 5. Pharmacologic Treatment of Asthma

Step	Age Group (yr)	Long-term Control (Daily Use)	Quick Relief
1	≥ 12	Preferred: Low-dose ICS + formoterol PRN Alternative: Low-dose ICS when SABA used	Preferred: Low-dose ICS + formoterol PRN Alternative: SABA PRN
	6–11	Preferred: No daily controller Alternative: Low-dose ICS when SABA used	SABA PRN
	0–5	Preferred: No daily controller	SABA PRN
2	≥ 12	Preferred: Low-dose ICS daily or low-dose ICS + formoterol PRN Alternative: LTM or low-dose ICS when SABA used	Preferred: Low-dose ICS + formoterol PRN Alternative: SABA PRN
	6–11	Preferred: Low-dose ICS Alternative: LTM or low-dose ICS when SABA used	SABA PRN
	0–5	Preferred: Low-dose ICS Alternative: LTM or intermittent ICS	SABA PRN
3	≥ 12	Preferred: Low-dose ICS + LABA Alternative: Medium-dose ICS or low-dose ICS + LTM	Preferred: Low-dose ICS + formoterol PRN Alternative: SABA PRN
	6–11	Preferred: Low-dose ICS + LABA or medium-dose ICS Alternative: Low-dose ICS + LTM	SABA PRN
	0–5	Preferred: Medium-dose ICS (double dosage for low-dose ICS) Alternative: Low-dose ICS + LTM	SABA PRN
4	≥ 12	Preferred: Medium-dose ICS + LABA Alternative: High-dose ICS, add-on tiotropium or LTM	Preferred: Low-dose ICS + formoterol PRN Alternative: SABA PRN
	6–11	Preferred: Medium-dose ICS + LABA Alternative: High-dose ICS + LABA or add-on tiotropium or LTM	SABA PRN
	0–5	Preferred: Continue controller and refer to specialist Alternative: Add LTM, increase ICS frequency, or add intermittent ICS	SABA PRN
5	≥ 12	Preferred: High-dose ICS + LABA and add-on tiotropium (history of exacerbation) or omalizumab (allergic asthma) or IL-5 antagonist (eosinophilic asthma) Alternative: Add low-dose OCS (consider adverse effects)	Preferred: Low-dose ICS + formoterol PRN Alternative: SABA PRN
	6–11	Preferred: Refer for phenotypic assessment Alternative: Add on IL-5 antagonist or low-dose OCS (consider adverse effects)	SABA PRN
	0–5	N/A	N/A

IL-5 = interleukin-5; LABA = long-acting β_2-agonist; LTM = leukotriene modifier; OCS = oral corticosteroid; PRN = as needed.

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2020. Available at www.ginasthma.org/. Accessed August 23, 2020.

G. Pharmacologic Therapy for Asthma (Tables 6 and 7)

Table 6. Pharmacologic Agents Used for Asthma and COPD

Generic	Brand	Dose	Adverse Effects	Comments
ICSs				
Beclomethasone MDI 40 mcg/puff 80 mcg/puff	QVAR RediHaler (breath activated)	See ICS dosing table	Inhaled Oral candidiasis Hoarseness May slow bone growth in children but similar adult height	ICSs are first line for persistent asthma Use holding chambers only if needed for technique; not needed or well studied with HFA inhalers; holding chambers are only for MDIs, cannot be used for DPIs; holding chamber with a mask can be used for young children Rinse mouth with water (and spit) after inhalations Use corticosteroid inhaler as scheduled, not as needed Onset of improvement is 5–7 days; additional benefit may occur over several weeks Pulmicort Respules are the only nebulized steroid available Arnuity Ellipta inhalation powder is contraindicated in severe hypersensitivity to milk proteins ArmonAir RespiClick has been discontinued in the United States for > 1 yr
Budesonide DPI 90 mcg/puff 180 mcg/puff Budesonide inhalation solution 0.25/2 mL 0.5/2 mL 1-mg/2-mL	Pulmicort Flexhaler Pulmicort Respules			
Ciclesonide MDI 80 mcg/puff 160 mcg/puff	Alvesco HFA			
Fluticasone propionate MDI 44 mcg/puff 110 mcg/puff 220 mcg/puff Fluticasone propionate DPI 50 mcg/puff 100 mcg/puff 250 mcg/puff Fluticasone furoate DPI 50 mcg/puff 100 mcg/puff 200 mcg/puff Fluticasone propionate DPI 55 mcg/puff 113 mcg/puff 232 mcg/puff	Flovent HFA Flovent Diskus Arnuity Ellipta 1 inhalation once daily ArmonAir Digihaler			
Mometasone DPI 110 mcg/puff 220 mcg/puff Mometasone MDI 50 mcg/puff 100 mcg/puff 200 mcg/puff	Asmanex Twisthaler Can be used once daily Asmanex HFA			
SAMAs				
Ipratropium MDI 17 mcg/puff Ipratropium inhalation solution 0.5 mg/2.5 mL	Atrovent HFA	2 puffs QID (up to 12 puffs/24 hr) 0.5 mg every 6–8 hr	Headache Flushed skin Blurred vision Tachycardia Palpitations	Used mainly for COPD and for acute asthma exacerbations necessitating emergency treatment

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
LAMAs				
Aclidinium bromide DPI 400 mcg/puff	Tudorza Pressair	1 puff BID	Headache Flushed skin Blurred vision Tachycardia Palpitations Acute urinary retention Cough (Respimat device)	LAMA for COPD
Glycopyrrolate DPI 15.6 mcg/capsule	Seebri Neohaler	Inhale contents of one capsule twice daily		LAMA approved for COPD
Glycopyrrolate inhalation solution 25 mcg/vial	Lonhala Magnair	Inhale one vial (25 mcg) twice daily		Only used with PARI nebulizer
Revefenacin inhalation solution 175 mcg/vial	Yupelri	Inhale 1 vial (175 mcg) once daily	Cough, nasopharyngitis, URTI, headache, back pain	Once-daily nebulized LAMA; for use with standard jet nebulizer
Tiotropium DPI 18 mcg/capsule	Spiriva HandiHaler	Inhale contents of 1 capsule/day		Spiriva Respimat is the only LAMA indicated for long-term maintenance treatment of asthma for those ≥ 12
Tiotropium inhalation spray 1.25 mcg/spray (asthma) 2.5 mcg/spray (COPD)	Spiriva Respimat	2 puffs once daily		
Umeclidinium DPI 62.5 mcg/blister	Incruse Ellipta	1 inhalation once daily		Once-daily LAMA for COPD
SABAs				
Albuterol MDI 90 mcg/spray	Proventil HFA Ventolin HFA ProAir HFA ProAir RespiClick DPI ProAir Digihaler DPI	2 puffs every 4–6 hr PRN	Tremor Tachycardia (less with levalbuterol) Hypokalemia Hypomagnesemia Hyperglycemia Tachyphylaxis *R*-enantiomer of albuterol	Used for acute bronchospasm; regular use indicates poor control Duration of effect (MDI): 3–4 hr (£ 6)
Albuterol inhalation solution 0.63 mg/3 mL 2.5 mg/3 mL 2.5 mg/0.5 mL		2.5 mg three or four times daily PRN	Duration (MDI): 3–4 hr (<6)	
Levalbuterol MDI 45 mcg/spray	Xopenex, generic	2 puffs every 4–6 hr PRN		
Levalbuterol inhalation solution 0.63 mg/3 mL		0.63 mg TID every 6–8 hr Maximum: 1.25 mg TID		

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
LABAs				
Arformoterol inhalation solution 15 mcg/2 mL	Brovana	Inhale 1 vial BID		Arformoterol is the *R,R*-isomer of racemic formoterol
Formoterol inhalation solution 20 mcg/2 mL	Perforomist	Inhale 1 vial BID		Onset of action 1–3 min but should not be used as acute therapy Should not be used as monotherapy for asthma
Indacaterol DPI 75-mcg capsule	Arcapta Neohaler	Inhale 1 capsule once daily		Indicated only for COPD Duration of action: 24 hr
Olodaterol inhalation spray 2.5 mcg/spray	Striverdi Respimat	2 puffs once daily		Indicated only for COPD Duration of action: 24 hr
Salmeterol DPI 50 mcg/puff	Serevent Diskus	Inhale 1 blister/puff BID		Not for acute symptoms Should not be used as monotherapy for asthma Duration: 8–12 hr
Combination SABA/SAMA				
Albuterol/ipratropium 100 mcg/20 mcg/puff	Combivent Respimat	1 puff QID Maximum dose 6 puffs/day	Cough Dyspnea HA Bronchitis Nasopharyngitis URTI	Used primarily for COPD
Ipratropium/albuterol inhalation solution 0.5 mg–3 mg/3 mL	DuoNeb	1 vial every 4–6 hr		
Combination LAMA/LABA				
Aclidinium/formoterol DPI 400 mcg/12 mcg	Duaklir Pressair	1 inhalation BID	URTIs, headache, back pain	Used for maintenance of COPD
Indacaterol/glycopyrrolate DPI 27.5 mcg/15.6 mcg/capsule	Utibron Neohaler	1 capsule inhaled BID	Nasopharyngitis	
Glycopyrrolate/formoterol fumarate DPI 9 mcg/4.8 mcg/spray	Bevespi Aerosphere	2 inhalations BID	Urinary tract infections Cough	
Tiotropium/olodaterol inhalation spray 2.5 mcg/2.5 mcg/spray	Stiolto Respimat	2 inhalations once daily		
Umeclidinium/vilanterol DPI 62.5 mcg/25 mcg/puff	Anoro Ellipta	1 inhalation once daily		

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
Combination ICS/LABA				
Budesonide/formoterol MDI 80 mcg/4.5 mcg/puff 160 mcg/4.5 mcg/puff	Symbicort (generic available)	2 puffs BID	Nasopharyngitis HA URTI Sinusitis Oral candidiasis Vomiting Influenza Back pain	GINA guidelines include use of low-dose budesonide/formoterol PRN for patients with mild intermittent asthma, including patients already taking it as a controller and those not taking a scheduled LABA/ICS regimen; not in NHLBI guidelines
Fluticasone/salmeterol DPI 100 mcg/50 mcg/puff 250 mcg/50 mcg/puff 500 mcg/50 mcg/puff	Advair Diskus Wixela Inhub (generic available)	1 puff BID	URTI Pharyngitis Dysphonia Oral candidiasis Cough HA N/V	
Fluticasone/salmeterol MDI 45 mcg/21 mcg/puff 115 mcg/21 mcg/puff 230 mcg/21 mcg/puff	Advair HFA	2 puffs BID	URTI Throat irritation Dysphonia HA Dizziness N/V	
Fluticasone propionate/salmeterol DPI 55 mcg/14 mcg/puff 113 mcg/14 mcg/puff 232 mcg/14 mcg/puff	AirDuo RespiClick AirDuo Digihaler	One inhalation twice daily	Nasopharyngitis Oral candidiasis Back pain HA Cough	Not FDA-approved for COPD Generic equivalent of AirDuo is available
Fluticasone furoate/vilanterol DPI 100 mcg/25 mcg 200 mcg/25 mcg	Breo Ellipta	1 inhalation once daily	Nasopharyngitis URTI HA Oral candidiasis Back pain Influenza Dysphonia Cough Pharyngitis	
Mometasone/formoterol DPI 100 mcg/5 mcg/puff 200 mcg/5 mcg/puff	Dulera	2 puffs BID	Nasopharyngitis Sinusitis HA	Not FDA-approved for COPD
Combination ICS/LAMA/LABA				
Fluticasone furoate/umeclidinium/vilanterol DPI 100 mcg/62.5 mcg/25 mcg/blister	Trelegy Ellipta	One inhalation once daily	URTI Pneumonia Bronchitis Oral candidiasis HA Back pain Arthralgia Influenza Sinusitis	
Budesonide/glycopyrrolate/formoterol MDI 160/9/4.8 mcg/puff	Breztri Aerosphere	2 puffs BID	URTI Pneumonia Back pain Oral candidiasis Influenza Muscle spasm Cough Sinusitis	Approved July 2020

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
LTMs				
Montelukast Oral 10-mg tablet Chewable 4- and 5-mg tablets Oral granules 4 mg/packet	Singulair	Dose in the evening Adults and those ≥ 15 yr: 10 mg/day Children 6 to < 15 yr: 5 mg/day Children 1 to < 6 yr: 4 mg/day	Headache GI upset Hepatotoxicity (zafirlukast and zileuton only) Zafirlukast: Monitor symptoms, may consider regular LFT monitoring but not needed Zileuton: Monitor LFTs (baseline, every month × 3 mo, every 2–3 mo for remainder of first year) *In March 2020, FDA added a boxed warning for montelukast because of the risk of serious neuropsychiatric events	Also indicated in exercise-induced bronchospasm and seasonal and perennial allergic rhinitis Drug interactions: Phenobarbital FDA approved for use in children ≥ 1 yr; used in children ≥ 6 mo Churg-Strauss syndrome associated with tapering doses of steroids
Zafirlukast 10-mg tablet 20-mg tablet	Accolate	10–20 mg BID		Drug interactions: Warfarin, erythromycin, theophylline FDA approved for children ≥ 5 yr Bioavailability decreases with food; take 1 hr before or 2 hr after meals
Zileuton 600-mg ER tablet	Zyflo	1200 mg BID		Drug interactions: warfarin, theophylline Only for those ≥ 12 yr
Monoclonal antibody/IgE–binding inhibitor				
Omalizumab	Xolair	150–375 mg SC every 2–4 wk Dose and frequency based on baseline IgE and weight in kilograms Do not inject > 150 mg per injection site	Injection site reactions: Urticaria Thrombocytopenia (transient) Anaphylaxis (rare) Malignancy	September 2014: New FDA Drug Safety Communication. Slightly increased risk of cardiovascular and cerebrovascular serious adverse events, including MI, unstable angina, TIA, PE/DVT, pulmonary HTN; no increased risk of stroke or CV death Used in severe persistent allergy-related asthma Use in those ≥ 12 yr Half-life: 26 days Second-line therapy Expensive
IL-4 antagonist				
Dupilumab	Dupixent	400 mg SC x 1; then 200 mg SC every other week OR 600 mg SC x 1; then 300 mg SC every other week (use higher dose if concomitant OCS required)	Hypersensitivity reaction Conjunctivitis and keratitis Injection site reactions Oropharyngeal pain Eosinophilia	Use in those ≥ 12 yr Indicated as add-on in those with eosinophilic asthma or who are OCS-dependent Avoid use of live vaccines

Table 6. Pharmacologic Agents Used for Asthma and COPD *(Cont'd)*

Generic	Brand	Dose	Adverse Effects	Comments
IL-5 antagonist				
Mepolizumab	Nucala	100 mg SC every 4 wk in the upper arm, thigh, or abdomen (≥ 12 yr) 40 mg SC every 4 wk (6–11 yr)	Injection-site reactions: Headache Fatigue Herpes zoster infection Hypersensitivity reaction (rare)	FDA-approved November 2015 Add-on maintenance therapy in severe asthma in ages ≥ 6 with an eosinophilic phenotype No eosinophil threshold is listed. However, data suggest that the absolute blood eosinophil count should be ≥ 150/mm^3 if patient is not taking daily systemic corticosteroids Reduces rate of asthma exacerbations by > 50%; reduces corticosteroid dose by 50%
Reslizumab	Cinqair	3 mg/kg IV infusion over 20–50 min every 4 wk	Increased creatine kinase concentration Myalgia Throat pain Anaphylaxis (rare)	FDA approved March 2016 Add-on maintenance therapy in severe asthma in those ≥ 18 with an eosinophilic phenotype In clinical trials, the eosinophilic phenotype was defined as a peripheral blood absolute eosinophil count of ≥ 400/mm^3 if patient not taking daily systemic corticosteroids Reduces rate of asthma exacerbations by about 50% in these patients
Benralizumab	Fasenra	30 mg SC every 4 wk for the first 3 doses, followed by once every 8 wk in upper arm, thigh, or abdomen	Headache Pharyngitis Fever Hypersensitivity reaction	FDA-approved November 2017 Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype

BID = twice daily; CV = cardiovascular; DPI = dry powder inhaler; DVT = deep venous thrombosis; ER = extended release; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; HA = headache; HFA = hydrofluoroalkane; HTN = hypertension; IgE = immunoglobulin E; IV = intravenous(ly); LA = long-acting; LAMA = long-acting anticholinergic/muscarinic antagonist; LFT = liver function test; MDI = metered dose inhaler; MI = myocardial infarction; N/V = nausea and vomiting; PE = pulmonary embolism; QID = four times daily; SAMA = short-acting anticholinergic/muscarinic antagonist; SC = subcutaneously; TIA = transient ischemic attack; TID = three times daily; URTI = upper respiratory tract infection.

Table 7. Inhaled Corticosteroid Daily Dosing in Children and Adults

Inhaled Corticosteroids: Available Products and Strengths (mcg unless noted)	**Low-Dose (mcg/day)**			**Medium-Dose (mcg/day)**			**High-Dose (mcg/day)**		
Age group (yr)	0–5	6–11	≥ 12	0–5	6–11	≥ 12	0–5	6–11	≥ 12
Beclomethasone QVAR HFA 40, 80	50 (age 5 only)	50–100	100–200	200 (age 5 only)	> 100–200	> 200–400	N/A	> 200	> 400
Budesonide Pulmicort DPI 90, 180	N/A	100–200	200–400	N/A	> 200–400	> 400–800	N/A	> 400	> 800
Budesonide suspension for nebulization Pulmicort Respules 250, 500, 1000	500	250–500	N/A	1000	> 500–1000	N/A	N/A	> 1000	N/A
Ciclesonide[a,b] Alvesco HFA 80, 160	N/A	80	80–160	N/A	> 80–160	> 160–320	> 160–320	> 160	> 320
Fluticasone Flovent HFA 50, 125, 250	50 (age ≥ 4)	50–100	100–250	100 (age ≥ 4)	> 100–200	> 250–500	N/A	> 200	> 500
Flovent DPI 50, 100, 250	N/A	50–100	100–250	N/A	> 100–200	> 250–500	N/A	> 200	> 500
Fluticasone furoate Arnuity Ellipta 50, 100, 200[a,c]	N/A	50	100	N/A	N/A	N/A	N/A	N/A	200
Mometasone Asmanex Twisthaler DPI 110, 220	110 (age ≥ 4)	110	110–220	220 (age ≥ 4)	> 220 – < 440	> 220–440	N/A	> 440	> 440
Asmanex HFA 50, 100, 200	100 (age 5 only)	100	200–400	N/A	N/A	N/A	N/A	200	> 400

[a]Doses are estimated from package insert.

[b]Ciclesonide was not available when the National Asthma Education and Prevention Program guidelines were published. The dose ranges are estimated from the package insert.

[c]Once daily.

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2020. Available at www.ginasthma.org/. Accessed August 23, 2020.

Patient Cases

Questions 1–3 pertain to the following case.

A 23-year-old woman has been coughing and wheezing about twice weekly, and she wakes up at night about three times per month. She has never been given a diagnosis of asthma and has not been to a physician, she says, "in years." She uses her roommate's albuterol inhaler, but having recently run out of refills, she is seeking care. Her activities are not limited by her symptoms. Spirometry today reveals FEV_1 82% of predicted.

1. According to the NAEPP guidelines, which is the best classification of her asthma?
   A. Intermittent.
   B. Mild persistent.
   C. Moderate persistent.
   D. Severe persistent.

2. Which medication is best to recommend for her, in addition to budesonide/formoterol MDI every 4–6 hours as needed?
   A. No additional therapy needed.
   B. Oral montelukast 10 mg/day.
   C. Mometasone DPI 220 mcg/puff 2 puffs daily.
   D. Budesonide/formoterol MDI 80/4.5 mcg per puff 2 puffs twice daily.

3. At first, the patient's symptoms were well controlled on your recommended therapy. However, when winter arrived, her symptoms were no longer well controlled, and she started using her albuterol 3 or 4 days per week during the day. Which is the preferred treatment change?
   A. No change in therapy is needed.
   B. Add fluticasone propionate/salmeterol DPI 55/14 mcg/puff 1 puff twice daily.
   C. Add montelukast orally 10 mg daily.
   D. Add mometasone DPI to 220 mcg/puff 2 puffs daily.

4. An 8-year-old boy has been having daytime asthma symptoms once or twice weekly and is awakened twice weekly at night with coughing. In addition to albuterol MDI 1 or 2 puffs every 4–6 hours as needed, which is the best initial therapy for him?
   A. Fluticasone MDI 44 mcg/puff 1 puff twice daily.
   B. Fluticasone MDI 110 mcg/puff 1 puff twice daily.
   C. Fluticasone/salmeterol DPI 100/50 mcg per puff 1 puff twice daily.
   D. Oral montelukast 10 mg/day.

H. Types of Inhalation Devices (Table 8)

Table 8. Different Types of Inhalation Devices

Type and Name[a]	Specifics	Type of Inhalation	Shake or Prime	Dose Counter	Advantages and Limitations
MDIs					
HFA inhalers: ProAir, Ventolin, Proventil, Xopenex, Flovent, Alvesco, Asmanex HFA, Symbicort, Dulera, Advair HFA, Atrovent, Aerosphere (Bevespi, Breztri) Breath Actuated (QVAR RediHaler)	Drug is mixed with a propellant	Press down canister at the start of a slow, deep inhalation	Prime: Yes Shake: Yes	Yes, except Proventil, Xopenex, Alvesco	Benefits: Slow, deep breath is easier than forceful, quick breath; may be used with a spacer or holding chamber Limitation: Requires coordination; many people have difficulty with technique
Single Dose System DPIs					
HandiHaler (Spiriva) Neohaler (Arcapta, Utibron, Seebri)	Individual gelatin capsules containing drug must be inserted and pierced before each use and removed after each use	Inhalation should be a steady and deep breath, enough to hear the whirring sound of the capsule rattling. Inhalation does not need to be as forceful as with some DPIs. May take a second inhalation if powder remains in the capsule	Prime: No Shake: No	No But not needed	Benefit: Inhalation is easier because it does not have to be forceful Limitation: Need to load and pierce each capsule before use
Preloaded Multidose DPIs					
Pressair (Tudorza, Duaklir) Twisthaler (Asmanex) Flexhaler (Pulmicort) Diskus (Advair, Flovent, Serevent)	Multiple doses are included in each device, either as a reservoir or a multiunit dose; each device lasts about 1 mo	Inhalation is quick, forceful, and deep; deeper and more forceful than in single-dose systems	Prime: No, except Flexhaler Shake: No	Yes	Benefit: No need to load capsules before each inhalation Limitation: Inhalation is more difficult to do correctly because it must be quick and forceful
Ellipta (Anoro, Breo, Arnuity, Incruse)	Different multidose system; 2 separate blister strips that dispense inhalation powder Contraindicated in severe hypersensitivity to milk protein	Inhalation is deep and slow, not fast and forceful as with other DPIs	Prime: No Shake: No	Yes	Benefits: Easier inhalation than with other DPIs; no need to load capsules before each inhalation; once-daily dosing with only 1 inhalation each time, all medications that come in the Ellipta device are 1 inhalation once daily

Table 8. Different Types of Inhalation Devices *(Cont'd)*

Type and Name[a]	Specifics	Type of Inhalation	Shake or Prime	Dose Counter	Advantages and Limitations
Breath-Actuated DPI					
Respiclick (ProAir, AirDuo Discontinued in the United States > 1 yr ago) Digihaler (ProAir, AirDuo, ArmonAir)	Medication is automatically released on inhalation; canister is not pressed Digihaler is the first digital inhaler with built-in sensors that measure inspiratory flow and detect inhaler use when the cap is opened or the patient inhales. Information is sent wirelessly to the companion mobile app using Bluetooth technology	Deep breath; quickly and deeply with enough force for the medication to be released Cannot be used with a spacer or holding chamber Contraindicated in severe hypersensitivity to milk proteins	Prime: No Shake: No	Yes	Benefit: No need to coordinate breath with actuation as with all other albuterol devices (MDIs)
Soft Mist Inhaler					
Respimat (Combivent, Spiriva, Striverdi, Stiolto)	Dose of drug is in solution and is released through a nozzle with jets of mist Lung deposition and amount of drug delivered are independent of the patient's effort	Inhalation is slow and deep	Prime: Yes Each new inhaler needs to be assembled, readied, and primed before first use; this is somewhat complicated If not used in 3 days, prime with 1 inhalation released into air Full repriming needed if not used in 21 days. Shake: No	Yes	Benefits: Ease of inhalation, consistent drug delivery Limitation: Complicated steps to ready and prime inhaler each month and after not using for 21 days

[a]For generic names and drug class, see Table 6.

I. Adjusting Asthma Treatment
   1. Control-based asthma management:
      a. Continuous cycle of treatment adjustment that involves assessment, treatment, and review
         i. Assess: Confirm diagnosis, symptom control and modifiable risk factors, comorbidities, inhaler technique, patient goals
         ii. Adjust: Treatment of modifiable risk factors and comorbidities, nonpharmacologic strategies, education and skills training, asthma medications
         iii. Review response: Symptoms, exacerbations, adverse effects, lung function, patient satisfaction
      b. Change in treatment on the basis of features of poor symptom control with or without other risk factors
      c. Accounts for both symptom control and future risk when choosing an asthma treatment
      d. Recommended approach to monitoring and adjusting treatment

2. Sputum eosinophil count:
    a. In adults, leads to reduced exacerbations and similar levels of symptom control
    b. Limited availability of routine sputum analysis
    c. Recommended for adults with moderate or severe asthma who are in treatment centers that have experience with this technique
3. FeNO
    a. In children/young adults, has been associated with reduced exacerbations
    b. In nonsmoking adults, no significant reduction in exacerbations
    c. Further study needed to identify populations most likely to benefit from FeNO-guided treatment

J. Use of Long-Acting Antimuscarinic Antagonists (LAMAs) for Asthma
1. Tiotropium Respimat is the only LAMA indicated for long-term treatment of asthma.
2. Tiotropium is approved as add-on therapy in patients with asthma age 6 years and older.
3. Recommended as an alternative add-on in step 4 because of insufficient evidence compared with ICS plus LABA
4. A preferred add-on in step 5
5. Evidence shows improved lung function and increased time to severe exacerbation.

K. Pharmacologic Treatment of Patients with Clinical Features of Asthma and COPD
1. If there are more features of asthma, use the treatment strategy for asthma.
2. If there are more features of COPD, use the treatment strategy for COPD.
3. If the clinical presentation includes features of both asthma and COPD, start with a low- or moderate-dose ICS and usually add a LABA or LAMA (www.ginasthma.org).

L. Long-Acting β_2-Agonists (LABAs): According to a U.S. Food and Drug Administration (FDA) safety announcement, issued because of safety concerns with LABAs (FDA Drug Safety Communication 2010):
1. Use of a LABA alone without a long-term asthma control drug such as an ICS is contraindicated because of an increased risk of severe worsening of asthma symptoms, leading to hospitalization and death in some children and adults.
2. LABAs should not be used in patients whose asthma is adequately controlled by low- or medium-dose ICSs.
3. LABAs should be used only as additional therapy for patients who are currently taking, but whose asthma is not adequately controlled by, a long-term asthma control agent (e.g., an ICS). An FDA review found no significant increase in risk of serious asthma outcomes with LABA use in combination with ICS (FDA Drug Safety Communication. 2017)
4. Once asthma control is achieved and maintained, patients should be assessed at regular intervals and stepped down (e.g., LABAs discontinued), if possible, and the patients should continue to be treated with a long-term asthma control agent (e.g., an ICS).
5. Pediatric and adolescent patients who need a LABA and an ICS should use a combination product to ensure adherence to both medications.

M. Exercise-Induced Bronchospasm: Diagnosis, Prevention, and Treatment of Symptoms
1. History of cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercise are suggestive of exercise-induced bronchospasm.
2. An exercise challenge can establish a diagnosis.
3. Long-term control therapy, if otherwise appropriate (initiate or step-up), should be used, particularly if exercise-induced bronchospasm is frequent or severe.
4. Pretreatment with SABA or low-dose ICS-formoterol and as needed for symptom relief is recommended.
5. Leukotriene modifiers (LTMs) can attenuate symptoms in 50% of patients, but onset is hours after administration.

N. Monitoring
   1. Peak flow monitoring
      a. Symptom-based and peak flow–based monitoring have similar benefits; either is appropriate for most patients. Symptom-based monitoring is more convenient.
      b. Daily home peak flow monitoring may be considered for moderate to severe persistent asthma if the patient has a history of severe exacerbations or has poor perception of worsening of asthma symptoms.
      c. Personal best peak expiratory flow rate (PEFR), not predicted PEFR, should be determined if a peak flow–based asthma action plan is being used.
         i. Personal best PEFR is the highest number attained after daily monitoring for 2 weeks twice daily when asthma is under good control.
         ii. Predicted PEFR is based on population norms for sex, height, and age.
   2. Spirometry (only used in patients 5 years and older)
      a. At initial assessment
      b. After treatment is started and symptoms are stabilized (3–6 months)
      c. If prolonged or progressive loss of asthma control
      d. At least every 2 years or more often, depending on response to therapy

O. Asthma Action Plan (Table 9)
   1. Usually symptom based (equal benefits of symptom-based and peak flow–based monitoring)
   2. Permits home treatment of an asthma exacerbation
   3. For all patients with early/mild symptoms:
      a. Increase reliever
      b. Provide early increase in controller
      c. Review response
   4. For late/severe symptoms if peak expiratory flow or FEV_1 less than 60% best, or symptoms not improving after 48 hours:
      a. Continue reliever
      b. Continue controller
      c. Add prednisone 40–50 mg/day
      d. Contact physician
   5. After initial treatment, immediate medical attention is needed if patient is at high risk of a fatal attack. Risk factors: asthma-related (history of severe attack [previous intubation or intensive care unit admission for asthma], ≥ 2 hospitalizations for asthma in past year, ≥ 3 ED visits for asthma in the past year, hospitalization or ED visit for asthma in the past month, using > 2 canisters of SABA a month, difficulty perceiving asthma symptoms), social (low socioeconomic status or inner-city residence, illicit drug use, major psychosocial problems), and comorbidities (cardiovascular disease, other chronic lung disease, chronic psychiatric disease).

Table 9. Asthma Action Plan

Zone	Signs and Symptoms	Treatment
Green	Doing well; no or minimal symptoms of coughing, wheezing, or dyspnea PEFR 80%–100% of personal best	Take long-term asthma control agent only (if one is prescribed) Use reliever inhaler 5–15 min before exercise if exercise-induced asthma and before known triggers Avoid things that make asthma worse
Yellow	Getting worse; increased frequency of symptoms (e.g., coughing, wheezing, chest tightness, or dyspnea); nighttime awakenings; decreased ability to engage in normal activities PEFR 50%–79% of personal best	Increase usual reliever (low-dose ICS-formoterol; increase frequency to max of 72 mcg formoterol/day; SABA: 2–4 puffs by MDI or 1 nebulizer treatment and repeat in 20 min, if needed). If complete response at 1 hr, contact clinician for follow-up instructions and consider OCS burst[a] If incomplete response in 1 hr (still some coughing, wheezing, or dyspnea), repeat SABA and add OCS burst; contact clinician that day for further instructions If poor response in 1 hr (e.g., marked coughing, wheezing, or dyspnea), repeat SABA immediately; add OCS burst; contact clinician immediately; proceed to the ED if the distress is severe and unresponsive to treatment; consider calling 911 May continue to use SABA every 3–4 hr regularly for 24–48 hr
Red	Medical alert (e.g., marked coughing, wheezing, or dyspnea); inability to speak more than short phrases; use of accessory respiratory muscles; drowsiness PEFR < 50% of personal best	Begin treatment and consult clinician immediately Increase usual reliever (low-dose ICS-formoterol; increase frequency to max of 72 mcg formoterol/day; SABA: 2–6 puffs by MDI or 1 nebulizer treatment) If incomplete or poor response, repeat SABA immediately; proceed to the ED or call 911 if distress is severe and unresponsive to treatment Call 911 or go to the ED immediately if lips or fingernails are blue or gray or if there is trouble walking or talking because of shortness of breath Continue using SABA every 3–4 hr regularly for 24–48 hr

[a]OCS burst: prednisone (or equivalent) 40–60 mg/day for 5–7 days (adults) or 1–2 mg/kg/day (maximum 40 mg/day) for 3–5 days (children).

ED = emergency department; PEFR = peak expiratory flow rate.

P. Managing Exacerbations: Initial—Emergency Department (ED) or Hospital (Table 10)

Table 10. Classifying Severity of Asthma Exacerbations in the Urgent or Emergency Care Setting[a]

Severity	Symptoms and Signs	Initial PEF or FEV_1[b]	Clinical Course
Mild or moderate	Talks in phrases, prefers sitting to lying, respiratory rate increased, heart rate 100–120 beats/min, Sa_{O_2} (room air) 90%–95%	> 50% predicted or personal best	Usually cared for at home or office visit; relief from frequently inhaled SABA; likely short course of ICS; some symptoms last 1–2 days after treatment begins
Severe	Dyspnea at rest; interferes with conversation; sits hunched forward; agitated; heart rate > 120 beats/min; respiratory rate > 30 breaths/min; use of accessory muscles; Sa_{O_2} (room air) < 90%	≤ 50% of predicted or personal best	Usually requires ED visit and likely hospitalization Partial relief from frequent inhaled SABA Oral systemic corticosteroids; some symptoms last > 3 days after treatment is begun Adjunctive therapies are helpful
Life-threatening	Too dyspneic to speak, perspiring; drowsy; confused	< 25% of predicted or personal best	Requires ED or hospitalization, possible ICU Little or no relief from frequent inhaled SABAs IV corticosteroids Adjunctive therapies are helpful

[a]For all ages.

[b]Lung function measures (PEF or FEV_1) may be useful for children ≥ 5 yr but may not be attainable in children during an exacerbation.

ICU = intensive care unit; PEF = peak expiratory flow.

Adapted from: Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention 2020. Available at www.ginasthma.org/. Accessed August 23, 2020.

1. Mild to moderate exacerbation (FEV_1 of 50% or more)
   a. Oxygen to achieve oxygen saturation (Sa_{O_2}) of 93%–98% (greater than 95% in pregnant women and those with concomitant heart disease)
   b. Inhaled SABA (MDI with valved holding chamber or nebulizer) up to three doses in the first hour
      i. Adult dose: albuterol MDI 4–10 puffs every 20 minutes for up to 4 hours, then every 1–4 hours as needed or by nebulizer 2.5–5 mg every 20 minutes for three doses, then 2.5–10 mg every 1–4 hours as needed
      ii. Pediatric dose (12 years or younger): albuterol MDI 4–8 puffs every 20 minutes for three doses, then every 1–4 hours as needed; use holding chamber (add mask if younger than 4 years) or by nebulizer 0.15 mg/kg (minimal dose 2.5 mg) every 20 minutes for three doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed
   c. OCS if no response immediately or if patient recently took an OCS
2. Severe exacerbation (FEV_1 of 50% or less)
   a. Oxygen to achieve Sa_{O_2} of 93%–98% (more than 95% in pregnant women and those with concomitant heart disease)
   b. High-dose inhaled SABA plus ipratropium by MDI plus valved holding chamber or nebulizer every 20 minutes or continuously for 1 hour

c. Oral corticosteroids
   i. Adult dose: Prednisone 40–50 mg/day in one or two divided doses until peak expiratory flow reaches 70% of predicted
   ii. Pediatric dose (12 years or younger): 1–2 mg/kg in two divided doses (maximum 40 mg/day) until peak expiratory flow reaches 70% of predicted
d. Consider adjunctive therapies (intravenous magnesium, intravenous ketamine, or heliox) if the patient is still unresponsive.

3. Impending or actual respiratory arrest
   a. Intubation and mechanical ventilation with oxygen 100%
   b. Nebulized SABA plus ipratropium
   c. Intravenous corticosteroids
   d. Consider adjunctive therapies (intravenous magnesium or heliox) if the patient is still unresponsive to therapy.
   e. Admission to intensive care

Q. Managing Exacerbations: ED or Hospital After Repeat Assessment
1. Moderate exacerbation (FEV_1 greater than 50%)
   a. Inhaled SABA every 60 minutes
   b. Oral corticosteroid
   c. Continue treatment for 1–3 hours if improvement
2. Severe exacerbation (FEV_1 of 50% or less); no improvement after initial treatment
   a. Oxygen
   b. Nebulized SABA plus ipratropium; hourly or continuous
   c. Consideration of adjunctive therapies
3. If good response to above treatment and maintained for at least 60 minutes
   a. Continue inhaled SABA.
   b. Continue OCS course.
   c. Consider initiating an ICS (if patient is not already taking one).
   d. Discharge home.
4. If incomplete response, admit to hospital ward
   a. Continuation of inhaled SABA
   b. Systemic corticosteroids (oral or intravenous)
   c. Consideration of adjunctive therapies
5. If poor response, admit to intensive care
   a. Continuation of inhaled SABA, hourly or continuously
   b. Intravenous corticosteroid
   c. Consideration of adjunctive therapies
   d. Possible intubation and mechanical ventilation

Patient Case

5. A 25-year-old man presents to the ED with shortness of breath at rest. He is having trouble with conversation. He used 4 puffs of albuterol MDI at home, with no resolution of symptoms. His FEV_1 is 38% of predicted. Which therapy, in addition to oxygen, is best for him initially in the ED?

   A. Oxygen alone is sufficient.

   B. Give albuterol MDI 8 puffs every 20 minutes for 1 hour.

   C. Give albuterol plus ipratropium by nebulizer every 20 minutes for 1 hour, plus oral corticosteroids.

   D. Give albuterol plus ipratropium by nebulizer every 20 minutes for 1 hour, plus intravenous corticosteroids.

R. Additional Vaccines: Adults with asthma (19–64 years) should receive:
   1. The 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax) once; then follow U.S. Centers for Disease Control and Prevention (CDC) recommendations for pneumococcal vaccination at age 65 and older
   2. Influenza vaccine every fall or winter

S. Asthma in Pregnancy
   1. Asthma may worsen, improve, or stay the same during pregnancy.
   2. Asthma may increase the risk of perinatal mortality, hyperemesis, vaginal hemorrhage, preeclampsia, complicated labor, neonatal mortality, prematurity, and low-birth-weight infants, especially if it is uncontrolled. Risks are small and are not shown in all studies.
   3. Medications
      a. The preferred controller is budesonide ICS (only category B ICS); however, if asthma is well controlled on another ICS before pregnancy, it may be continued.
      b. The preferred rescue inhaler is albuterol.
      c. LABAs are category C, with less clinical experience. Use during pregnancy is reasonable if necessary for asthma control. Salmeterol is the preferred LABA.
      d. LTMs have limited data; most data are with montelukast (category B), and the data for montelukast are reassuring. These are considered an alternative therapy.
      e. Prednisone is category C; potential adverse effects in pregnancy are cleft palate, preeclampsia, gestational diabetes, low birth weight, and prematurity. However, few studies involved patients with asthma, and women might have been exposed to longer-term prednisone use. Prednisone should be used, if necessary, for acute exacerbations in pregnancy.

II. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Guidelines:

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD 2020. Available at www.goldcopd.org/. Accessed August 23, 2020.

A. Definition: COPD is a common, preventable, and treatable syndrome of persistent limitation in expiratory airflow encompassing both small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Airflow obstruction may be accompanied by airway hyperresponsiveness and may not be fully reversible. Airway and alveolar abnormalities are usually caused by significant exposure to noxious particles.
   1. Chronic bronchitis consists of persistent cough plus sputum production for most days of 3 months in at least 2 consecutive years and is an independent disease entity that may occur before or after the development of airflow limitation.
   2. Emphysema is abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. Emphysema is only one of several structural abnormalities in patients with COPD.

B. Diagnosis and Assessment
   1. The clinical diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with the presence of symptoms.
      a. Symptoms: Dyspnea (described by patients as "increased effort to breathe," "heaviness," "air hunger," or "gasping"), poor exercise tolerance, chronic cough, sputum production, wheezing

b. GOLD guidelines: Perform spirometry and consider COPD if a patient is older than 40 and has any of the following:
   i. Dyspnea that is progressive (worsens over time), persistent (present every day), and worse with exercise or on exertion
   ii. Chronic cough that is present intermittently or every day; often present throughout the day; seldom only nocturnal; may be nonproductive
   iii. Chronic sputum production in any pattern
   iv. History of exposure to risk factors, especially tobacco smoke (most common risk factor), occupational dusts and chemicals, and smoke from home cooking and heating fuels
c. American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) guidelines: The single best predictor of airflow obstruction is the presence of all three of the following:
   i. Smoking history of more than 55 pack-years
   ii. Wheezing on auscultation
   iii. Patient's self-report of wheezing

2. For the diagnosis and assessment of COPD, spirometry is the gold standard.
   a. Spirometry revealing an FEV_1/FVC less than 70% of predicted is the hallmark of COPD. Bronchodilator reversibility testing is no longer recommended.
   b. Measurement of arterial blood gas tension should be considered for all patients with FEV_1 less than 50% of predicted or clinical signs suggestive of respiratory failure or right heart failure.
   c. On the basis of the spirometry result, a GOLD grade is assigned. The GOLD grade is primarily used to direct nonpharmacologic interventions (e.g., pulmonary rehabilitation, lung reduction surgery).
      i. GOLD 1: Mild FEV 80% or greater of predicted
      ii. GOLD 2: Moderate FEV 50%–79% of predicted
      iii. GOLD 3: Severe FEV 30%–49% of predicted
      iv. GOLD 4: Very severe FEV less than 30% of predicted
3. Assess the frequency of exacerbations in the past 12 months:
   a. Less severe: 0 or 1 exacerbation (not leading to hospital admission)
   b. More severe: 2 or more exacerbations, or 1 or more exacerbation leading to hospital admission
4. Use validated symptom scales or questionnaires:
   a. The COPD Assessment Test (CAT) measures health status impairment in COPD (www.catestonline.org).
      i. Measures symptoms beyond breathlessness, such as cough, sputum production, chest tightness, limitation of activities, sleep, energy level, and confidence to leave house
      ii. Scale of 5 to more than 30
         (a) 5 is upper limit of normal.
         (b) Less than 10 is low impact on life.
         (c) More than 30 is high impact on life; can barely leave the house
   b. mMRC breathlessness scale for assessing severity of breathlessness (Thorax 1999;54:581-6)
      i. Measures severity of shortness of breath or breathlessness
      ii. Scale of 0–4
         (a) 0 = least symptoms; breathless only with strenuous exercise
         (b) 4 = too breathless to leave house; breathless even when dressing

C. Factors Determining Severity of COPD
   1. Severity of airflow limitation (FEV_1)
   2. Frequency and severity of exacerbations

3. Severity of symptoms (mMRC, CAT)
4. Presence of comorbidities that may restrict activity (e.g., heart failure, heart disease, musculoskeletal disorders, depression)

D. Therapy Goals
   1. Relieve symptoms.
   2. Reduce the frequency and severity of exacerbations.
   3. Improve exercise tolerance.
   4. Improve health status.
   5. Minimize adverse effects from treatment.

E. Management of Stable COPD
   1. Description of levels of evidence or grades of recommendations (Table 11)

Table 11. Grades for Strength of Recommendations for COPD Guidelines

GOLD Guidelines	
A	Randomized clinical trials Rich body of data
B	Randomized clinical trials Limited body of data
C	Nonrandomized trials Observational studies
D	Panel judgment consensus

GOLD = Global Initiative for Chronic Obstructive Lung Disease.

2. Existing medications for COPD have not been shown to modify the long-term decline in lung function, the hallmark of this disease (level of evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms, complications, or both.
3. Smoking cessation is a critical component of COPD management for patients who are actively using tobacco.
4. Bronchodilator medications are central to the symptomatic management of COPD (level of evidence A).
   a. Primary mechanism in COPD is through changes to smooth muscle tone that result in airway widening
   b. Can be given as needed or on a scheduled basis to prevent and reduce symptoms
   c. Principal treatments are: β_2-agonists, muscarinic antagonists, and a combination of these drugs
   d. Inhaled therapy is preferred to oral therapies because of less systemic exposure
   e. Combining agents from different classes may improve efficacy compared with increasing the dose of a single bronchodilator
   f. Short- or long-acting bronchodilator is recommended as initial treatment for all COPD groups (Table 12).
   g. Treatment with a LAMA delays first exacerbation, reduces the overall number of COPD exacerbations and related hospitalizations, improves symptoms and health status (level of evidence A), and improves the effectiveness of pulmonary rehabilitation (level of evidence B).
      i. No effect on the rate of lung function decline (no consistent or significant FEV_1 improvement)
      ii. Initial tiotropium studies reported increased cardiovascular risk, but currently available studies do not reproduce the findings.

h. LABAs improve health status, quality of life, and FEV_1 and decrease COPD exacerbation rate (level of evidence A).
   i. No effect on mortality or rate of lung function decline
   ii. Do not have the same potential safety concerns as in asthma management
   iii. Salmeterol significantly reduces hospitalization rate and treatment of exacerbations (level of evidence B).
   iv. Indacaterol has significantly greater bronchodilator effect than salmeterol, similar to that of tiotropium (level of evidence A).

i. LAMAs versus LABAs
   i. POET-COPD trial: Tiotropium was more effective than salmeterol as initial bronchodilator therapy in moderate to very severe COPD regarding time to first exacerbation and annual number of exacerbations (N Engl J Med 2011;364:1093-103).
   ii. Cochrane review: Tiotropium is more effective than LABAs in preventing COPD exacerbations and COPD-related hospitalization, but not in overall hospitalizations or mortality. Symptom and lung function improvement were similar. However, studies are sparse. Fewer serious adverse events and withdrawals from studies occurred with tiotropium than with LABAs (Cochrane Database Syst Rev 2012;9:CD009157).
   iii. FLAME trial: LAMA/LAMA (indacaterol/glycopyrrolate) had greater efficacy than LABA/ICS (salmeterol/fluticasone) in preventing COPD exacerbations in patients with a history of exacerbations in the previous year (N Engl J Med 2016;374:2222-34).

j. ICSs in Stable COPD
   i. Not recommended as monotherapy and may increase risk of mortality compared with use in combination treatment
   ii. Theoretically work as anti-inflammatory agents to decrease airway inflammation
   iii. Blood eosinophil counts may predict the magnitude of ICS effect in preventing future exacerbations
      (a) Some studies have found a greater risk of exacerbation after withdrawal of ICS when eosinophil count was greater than 300 cells/mcL (N Engl J Med 2014;371:1285-94; Am J Respir Crit Care Med 2018;198:329-39), whereas other studies have found no link between ICS withdrawal and increased exacerbation risk (Thorax 2005;60:480-7; Respir Res 2014;15:77).
      (b) Effect of an ICS on lung function, health status, and exacerbations is decreased when eosinophils are < 100 cells/mcL. Evidence is less clear regarding the efficacy of ICS with continued tobacco use.
   iv. Use is associated with an increased risk of pneumonia, oral candidiasis, and hoarse voice.
   v. In patients currently receiving LABA/ICS without documented benefit (symptom relief and/or reduction in exacerbations) or eosinophil-driven inflammation, clinicians should substitute a LAMA for ICS versus escalating to triple therapy (Respir Res 2017;18:140; Respirology 2018;23:1152-9).
   vi. Group C: ICS + LABA is alternative for treatment intensification when eosinophils > 300 cells/mcL and history of exacerbations
   vii. Group D: LAMA + LABA + ICS as treatment intensification when eosinophils > 100 cells/mcL; LABA + ICS as alternative initial treatment when eosinophils > 300 cells/mcL

k. Triple therapy:
   i. Shown to improve lung function and health-related quality of life while reducing the number of exacerbations
   ii. First available triple therapy single inhaler is available and contains an ICS (fluticasone furoate), LABA (vilanterol), and LAMA (umeclidinium)

iii. The FULFIL trial showed improvements in FEV_1 and moderate to severe exacerbations with triple therapy compared to ICS/LABA Am J Respir Crit Care Med 2017;196:438-46).
iv. IMPACT further demonstrated benefits of triple therapy compared to ICS/LABA and LAMA/LABA through lower rate of moderate to severe COPD exacerbations compared to both dual treatments and lower rate of COPD hospitalizations than LAMA/LABA. N Engl J Med 2018;378:1671-80).
v. In certain patients, adding tiotropium to a LABA/ICS combination (triple therapy) improves lung function and health-related quality of life and reduces the number of exacerbations (level of evidence B).

5. Patient assessment and selection of therapy
   a. GOLD guidelines combine symptoms (based on symptom scores) and frequency of exacerbations in the previous 12 months to determine patient risk group and recommend initial treatment (Figure 1 and Table 12).
   b. Maintenance therapy adjustments are recommended according to the predominant treatable trait of dyspnea (Table 13) or exacerbations (Table 14). These recommendations do not depend on the ABCD assessment at diagnosis and focus on current treatment. If both exacerbations and dyspnea need to be targeted, the exacerbation pathway should be followed.
   c. Peak inspiratory flow rate (PIFR) measured against the simulated resistance of a dry powder inhaler (DPI) is emerging as a way to further guide therapy and provide a patient-centered product recommendation. PIFR less than 60 mL/minute is considered suboptimal and may identify those with a suboptimal response to a DPI.

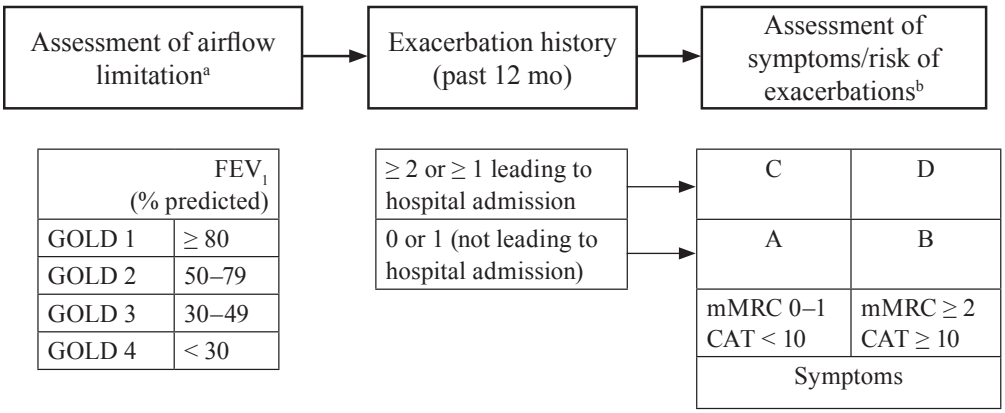


Figure 1. GOLD guidelines: refined assessment of COPD severity and risk.

[a]Post-bronchodilator FEV_1 should be used.

[b]CAT score is preferred, but any can be used.

CAT = COPD Assessment Test (validated questionnaire); GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified Medical Research Council breathlessness scale (validated questionnaire).

Adapted from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2020 Update. Available at www.goldcopd.org/. Accessed August 23, 2020.

Table 12. GOLD Guidelines: Initial Pharmacologic Treatment

Patient Group	Symptoms and Exacerbations	Recommended Initial Treatment
A	Few symptoms (CAT score < 10) No hospitalizations ≤ 1 exacerbation in the past year	Bronchodilator (short- or long-acting)
B	Many symptoms (CAT score ≥ 10) No hospitalizations ≤ 1 exacerbations in the past year	LABA or LAMA
C	Few symptoms (CAT score < 10) ≥ 1 COPD-related hospitalization or ≥ 2 exacerbations in the past year	LAMA
D	Many symptoms (CAT score ≥ 10) ≥ 1 COPD-related hospitalization or ≥ 2 exacerbations in the past year	LAMA or LAMA + LABA[a] or LABA + ICS[b]

[a]Consider if highly symptomatic (CAT > 20).

[b]Consider if eosinophils ≥ 300 cells/mcL.

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist.

Information from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2020.

Table 13. Follow-up Treatment for Dyspnea

Current Treatment	Recommended Treatment Change(s)
LABA or LAMA	LABA + LAMA If ineffective: consider changing inhaler devices or molecules, and investigate other causes of dyspnea
LABA + ICS	LABA + LAMA + ICS OR Consider de-escalation of ICS and change to LABA + LAMA[a]
LABA + LAMA + ICS	Consider de-escalation of ICS and change to LABA + LAMA[a] OR Consider changing inhaler devices or molecules, and investigate other causes of dyspnea

[a]Consider if pneumonia, inappropriate original indication, or lack of ICS response.

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist.

Information from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2020.

Table 14. Follow-up Treatment for Exacerbations

Current Treatment	Recommended Treatment Change(s)
LABA or LAMA	LABA + LAMA OR LABA + ICS[a]
LABA + ICS	LABA + LAMA + ICS OR Consider de-escalation of ICS and change to LABA + LAMA[b]
LABA + LAMA	LABA + LAMA + ICS[c] OR Consider adding roflumilast if FEV_1 < 50% and chronic bronchitis[d] AND/OR azithromycin daily if former smoker[d]
LABA + LAMA + ICS	Consider de-escalation of ICS and change to LABA + LAMA[b] OR Consider adding roflumilast if FEV_1 < 50% and chronic bronchitis AND/OR azithromycin daily if former smoker

[a]Consider if eosinophils ≥ 300 cells/mcL or ≥ 100 cells/mcL AND ≥ 2 exacerbations/1 hospitalization.

[b]Consider if pneumonia, inappropriate original indication, or lack of ICS response.

[c]Consider if eosinophils ≥ 100 cells/mcL.

[d]Consider if eosinophils < 100 cells/mcL.

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting anticholinergic/muscarinic antagonist.

Information from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2020.

6. Other pharmacologic treatments
    a. Phosphodiesterase type 4 (PDE-4) inhibitor: Roflumilast (Daliresp)
        i. Indication: PDE-4 inhibitors may be used as a daily treatment to reduce the risk of COPD exacerbations in patients with severe COPD (FEV_1 less than 50% of predicted) associated with chronic bronchitis and a history of frequent exacerbations despite treatment with LABA + LAMA + ICS, particularly if eosinophils are less than 100 cells/mcL. Studies show a reduction in exacerbations and a reduction in the composite end point of moderate exacerbations treated with oral or systemic corticosteroids or severe exacerbations necessitating hospitalization or causing death (level of evidence B). These effects also occur when roflumilast is added to LA bronchodilators (level of evidence B). No trials have assessed the effects of roflumilast on COPD exacerbations when added to an ICS/LA bronchodilator combination. No comparison of adding roflumilast versus ICS to LA bronchodilators is available (now being studied).
        ii. Reduces inflammation through inhibition of the breakdown of intracellular cyclic adenosine monophosphate; has no direct bronchodilator activity
        iii. Starting dose: 250 mcg orally once daily for four weeks and then increased to the maintenance dose of 500 mcg orally once daily, which may allow for better GI tolerance
        iv. Contraindicated in cases of moderate to severe liver impairment and in nursing mothers
        v. Can cause weight loss (monitor) and psychiatric events, including suicidality (monitor; weigh risk-benefit ratio in patients with preexisting psychiatric illness). Twenty percent of patients studied had weight loss of 5%–10% of body weight, compared with 7% with placebo; average weight loss was 2 kg.
        vi. Adverse reactions include diarrhea, weight loss or decreased appetite, nausea, headache, back pain, influenza, insomnia, and dizziness.

vii. Use with strong cytochrome P450 (CYP) enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended; use with CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine) increases roflumilast exposure and adverse effects (weigh risk-benefit ratio).

viii. According to the ACCP/CTS guidelines to prevent exacerbations, roflumilast is suggested for patients with moderate-severe COPD with chronic bronchitis and a history of at least 1 exacerbation in the past year.

b. Antibiotics – Azithromycin
   i. Actions are anti-inflammatory and antibacterial
   ii. Daily azithromycin at 250 mg orally daily for 1 year found to lengthen time to first exacerbation, decrease overall exacerbation rate, and improve quality of life (N Engl J Med 2011;365:689-98)
   iii. Azithromycin 500 mg orally 3 times per week and erythromycin 500 mg orally twice daily have reduced exacerbations (Lancet Respir Med 2014;2:361-8; N Engl J Med 2011;365:689-98)
   iv. Potential adverse effects include hearing loss (contradictory evidence), pneumonia, GI disturbances, and QTc prolongation
   v. Recommended as add-on to treatment intensification with LABA + LAMA +/- ICS if eosinophils < 100 cells/mcL and former smoker
c. Smoking cessation therapy (essential for all patients)
d. Vaccinations
   i. Influenza vaccine annually (essential for all patients)
   ii. PPSV23 (Pneumovax) once before age 65; then in accordance with CDC recommendations for pneumococcal vaccination at age 65 and older
   iii. The 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar) once after age 65 and at least 1 year after PPSV23
e. α_1-Antitrypsin augmentation therapy (level of evidence B)
   i. Once weekly intravenous therapy of an α_1-proteinase inhibitor (Aralast NP, Glassia, Prolastin-C, Zemaira)
   ii. For young patients with a severe hereditary α_1-antitrypsin deficiency and established emphysema.
   iii. Patients with an α_1-antitrypsin deficiency are usually white, usually have COPD at a young age (younger than 45), and have a strong family history. It may be worthwhile to screen patients with these characteristics for α1-antitrypsin deficiency.
   iv. α_1-Antitrypsin deficiency should be considered in patients with frequent COPD exacerbations (Cleve Clin J Med 2016;83:507-14).

Patient Cases

Questions 6 and 7 pertain to the following case.

A 62-year-old man was recently given a diagnosis of COPD. Spirometry reveals an FEV_1/FVC 60% of predicted, pre-bronchodilator FEV_1 70% of predicted, and post-bronchodilator FEV_1 72% of predicted. His symptoms are quite bothersome. He reports walking more slowly than others because of shortness of breath and having to stop to catch his breath every so often when walking on level ground (mMRC score 2). He had 1 exacerbation in the past year that did not require hospitalization.

6. Which is the most appropriate patient group classification for him, according to the GOLD guidelines?
   A. GOLD 1, group A.
   B. GOLD 2, group B.
   C. GOLD 3, group C.
   D. GOLD 4, group D.

7. In addition to albuterol 2 puffs every 4–6 hours as needed, which pharmacotherapy option is most appropriate to initiate?
   A. No additional therapy needed.
   B. Salmeterol 50 mcg 1 puff twice daily.
   C. Tiotropium/olodaterol 2.5/2.5 2 puffs once daily.
   D. Salmeterol/fluticasone 50/500 1 puff twice daily plus roflumilast 500 mcg orally once daily.

8. A 52-year-old woman with COPD reports a gradual worsening of shortness of breath during the past few years. Spirometry reveals FEV_1/FVC 55% and FEV_1 63% of predicted. Her CAT score is 10 and eosinophil count is 68 cells/mcL. She has not had a COPD exacerbation or received systemic corticosteroids in the past 2 years. Her current COPD medications are tiotropium inhaler once daily and albuterol HFA as needed. According to the GOLD guidelines, which is the most appropriate course of action?
   A. Adding salmeterol 50 mcg 1 puff twice daily.
   B. Adding long-term azithromycin 250 mg once daily.
   C. Adding fluticasone 110 mcg 2 puffs twice daily.
   D. Discontinuing tiotropium and initiating salmeterol/fluticasone 50 mcg/250 mcg 1 puff twice daily.

7. Nonpharmacologic therapy
   a. Home oxygen therapy
      i. Recommended in patients who have a PaO_2 of 55 mm Hg or less (or 55–60 mm Hg if pulmonary hypertension, peripheral edema, or polycythemia [level of evidence D]) or SaO_2 of 88% or less, with or without hypercapnia, confirmed twice during a 3-week period (level of evidence B)
      ii. Improved survival with long-term (more than 15 hours/day) use in patients with chronic respiratory failure
   b. Pulmonary rehabilitation (essential for patient groups B–D; level of evidence A)
      i. Includes exercise training, nutrition counseling, and education
      ii. Recommended when patients have moderate COPD instead of waiting until it is more severe
      iii. Improves many outcomes in COPD, including quality of life and survival

c. Lung cancer screening
    i. USPSTF recommends annual lung cancer screening for aged 55-80 years old who have a 30 pack-year smoking history and currently smoke or quit < 15 years ago.
    ii. Concern related to appropriateness of recommendations as lung cancer is leading cause of death in patients with COPD
    iii. It has been suggested to change to a > 1 pack-year threshold for patients with COPD to lead to a higher life expectancy than currently seen (Cancer 2015;121:1556-62).

8. Other medications
    a. β-Blockers
        i. Observational data suggest that long-term treatment with β-blockers reduces risk of exacerbations and improves survival, even in patients without overt cardiovascular disease (Arch Intern Med 2010;170:880-7).
            (a) More than half of the patients studied had cardiovascular risk factors or coronary artery disease.
            (b) Mostly cardioselective β-blockers were used.
        ii. β-Blockers should not currently be recommended for the treatment of COPD, but β-blockers should not be withheld in patients with COPD who also have heart disease, chronic heart failure, or other cardiovascular conditions in which β-blockers are beneficial (Cochrane Database Syst Rev 2005;4:CD003566).
        iii. The mechanism of benefit in COPD is unknown, but β-blockers can upregulate β_2-receptors in the lungs, which may improve the effectiveness of inhaled β-agonists.
    b. Statins
        i. Several retrospective studies have found benefits for statin use in COPD for reducing exacerbations and COPD-related mortality (Thorax 2015;70:33-40; Am J Respir Crit Care Med 2013;187:A6017; Am J Med 2013;126:598-606).
        ii. The STATCOPE trial found no significant effect of simvastatin on the number of severe COPD exacerbations per person-year compared with placebo (Chest 2015;147:894-942).
        iii. The Rotterdam trial found a 78% lower risk of mortality in patients with COPD and high-sensitivity C-reactive protein concentrations greater than 3 mg/dL, indicating a higher level of systemic inflammation (Pulm Pharmacol Ther 2013;26:212-7).
        iv. Authors of a meta-analysis involving 53 studies concluded that statins significantly reduced the risk of all-cause mortality by 28%, risk of COPD-associated mortality by 28%, and risk of acute COPD exacerbations by 16%. Authors hypothesized that statins decrease many inflammatory markers thought to play a role in COPD (CRP, IL-6, IL-8 and TNFα) (Respir Res 2019;20:Article 17).
        v. No strong prospective evidence exists to suggest statins provide a clinical benefit in patients with COPD without other cardiovascular disease risk factors.

F. Management of Acute Exacerbations of Chronic COPD
1. A COPD exacerbation is an acute worsening of a patient's baseline respiratory symptoms (e.g., dyspnea, cough, and/or an increase in quantity or purulence of sputum) that is worse than normal day-to-day variation and results in a change in medication. Diagnosis is based purely on clinical presentation.
2. Classification:
    a. Mild: SA bronchodilators only
    b. Moderate: SA bronchodilators plus antibiotics and/or oral corticosteroids
    c. Severe: hospitalization or ED visits
        i. No respiratory failure: respiratory rate of 20 to 30 breaths/minute; no accessory muscles; no mental status changes; hypoxemia improved with supplemental oxygen; no increase in $PaCO_2$

   ii. Acute respiratory failure, non–life-threatening: more than 30 breaths/minute; accessory respiratory muscles in use; no change in mental status; hypoxemia improved with supplemental oxygen; $PaCO_2$ increased compared to baseline
   iii. Acute respiratory failure, life-threatening: more than 30 breaths/minute; accessory respiratory muscles in use; acute changes in mental status; hypoxemia not improved with supplemental oxygen; $PaCO_2$ increased compared to baseline or pH of 7.25 or greater
3. Common precipitating factors include infection of the tracheobronchial tree and viral upper respiratory tract infections (most common) and air pollution. However, the cause of one-third of exacerbations cannot be determined.
4. Spirometry is inaccurate during an exacerbation and is not recommended.
5. Pulse oximetry can be used to determine the need for supplemental oxygen, which should be given in severe exacerbations. In exacerbations necessitating hospitalization, arterial blood gas measurement should be performed. Supplemental oxygen should be titrated to a target saturation of 88%–92% (BMJ 2010;341:c5462).
6. Inhaled bronchodilators (inhaled SABAs with or without SA anticholinergics) are the preferred treatment of COPD exacerbations (level of evidence C).
   a. The usual dose of albuterol is 2.5 mg by nebulizer every 1 to 4 hours as needed or 4 to 8 puffs by MDI with holding chamber every 1 to 4 hours as needed.
   b. SA anticholinergics (ipratropium) are generally added for acute exacerbations.
7. Systemic corticosteroids are effective, and they shorten recovery time, improve FEV_1, and improve hypoxemia (level of evidence A). They also lower the risk of treatment failure and early relapse rate and shorten hospital stays. Systemic corticosteroids should be used in most exacerbations. OCS dose for outpatient treatment: 40 mg of oral prednisone once daily for 5 days is recommended in the GOLD guidelines (level of evidence B), but insufficient data are available to provide strong conclusions about the optimal duration.
   a. Higher daily doses or oral prednisone/prednisolone may be used (e.g., 50–60 mg daily).
   b. A recent study showed that in patients with a COPD exacerbation presenting to the hospital, a shorter course of systemic corticosteroids (5 days) was non-inferior to a longer (14 days) course with respect to re-exacerbation within 6 months (JAMA 2013;309:2223-31).
8. Antibiotic treatment should be initiated for exacerbations if the criteria below are met. The most common pathogens in COPD exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In patients with GOLD 3 and 4 severity, *Pseudomonas aeruginosa* should be considered a potential pathogen.
   a. The three cardinal symptoms in COPD exacerbations are: increased dyspnea, increased sputum volume, and increased sputum purulence.
      i. Antibiotics should be given if all three cardinal symptoms are present (level of evidence B).
      ii. Antibiotics should be given if two of the three cardinal symptoms are present and if increased sputum purulence is one of the symptoms (level of evidence C).
      iii. Antibiotics should be given to patients with severe exacerbations requiring mechanical ventilation (level of evidence B).
   b. The recommended duration of antibiotic treatment is usually 5 to 7 days (level of evidence B).
   c. Recommended antibiotics
      i. Empiric treatment consists of amoxicillin with clavulanic acid, a macrolide (e.g., azithromycin), or a tetracycline (e.g., doxycycline). Antibiotic selection should be decided on using local susceptibility data and trends.
      ii. If antibiotics have been used recently (in the last 3 months), use an alternative class.
      iii. In complicated COPD with risk factors, amoxicillin/clavulanate, levofloxacin, and moxifloxacin are antibiotics of choice. Risk factors include comorbid diseases, severe COPD (FEV_1 less than 50% of predicted), more than three exacerbations/year, antibiotic use in past 3 months

iv. If the patient is at risk of *Pseudomonas* infection: Obtain sputum culture(s) and administer high-dose levofloxacin (750 mg) or ciprofloxacin. Risk factors include: Four or more antibiotic courses within the past year, recent hospitalization (in the past 90 days), isolation of *Pseudomonas* during past hospitalization(s), severe COPD (FEV_1 less than 50% of predicted)
v. If exacerbation does not respond to the initial antibiotic, sputum culture and sensitivity should be performed.

Patient Case

9. A 64-year-old woman with COPD in GOLD patient group A presents for a clinic visit. In the past few days, she has had a worsening of shortness of breath and a productive cough with more "cloudy" and more copious sputum than usual. Pulse oximetry is 95% on room air. She has a nebulizer at home. In addition to regular use of albuterol plus ipratropium by nebulizer every 1 to 4 hours, which is the best course of action?

   A. No additional therapy is necessary.

   B. Add oral prednisone 40 mg once daily for 5 days.

   C. Add azithromycin 500 mg daily for 3 days.

   D. Add oral prednisone 40 mg once daily for 5 days and azithromycin 500 mg daily for 3 days.

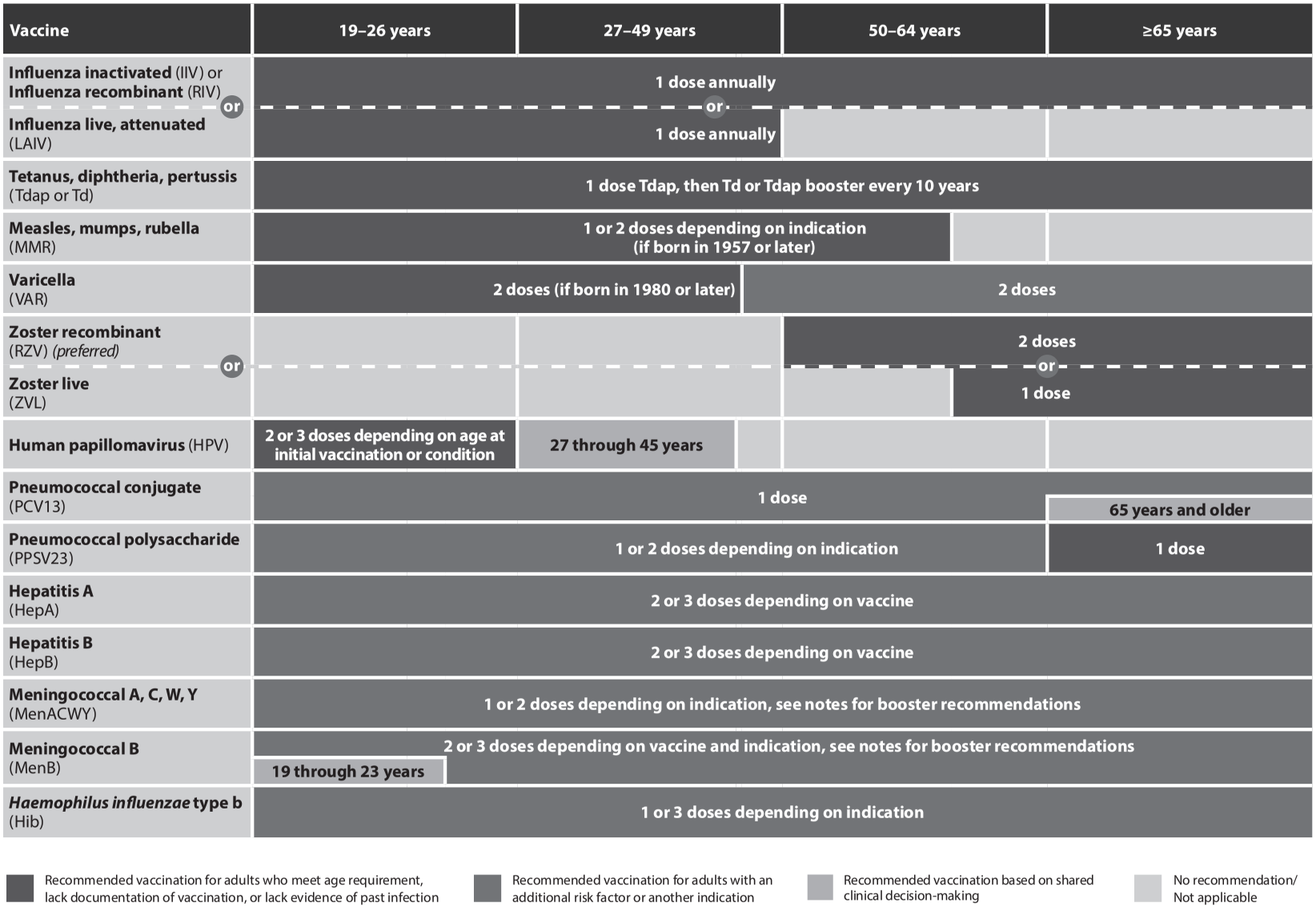
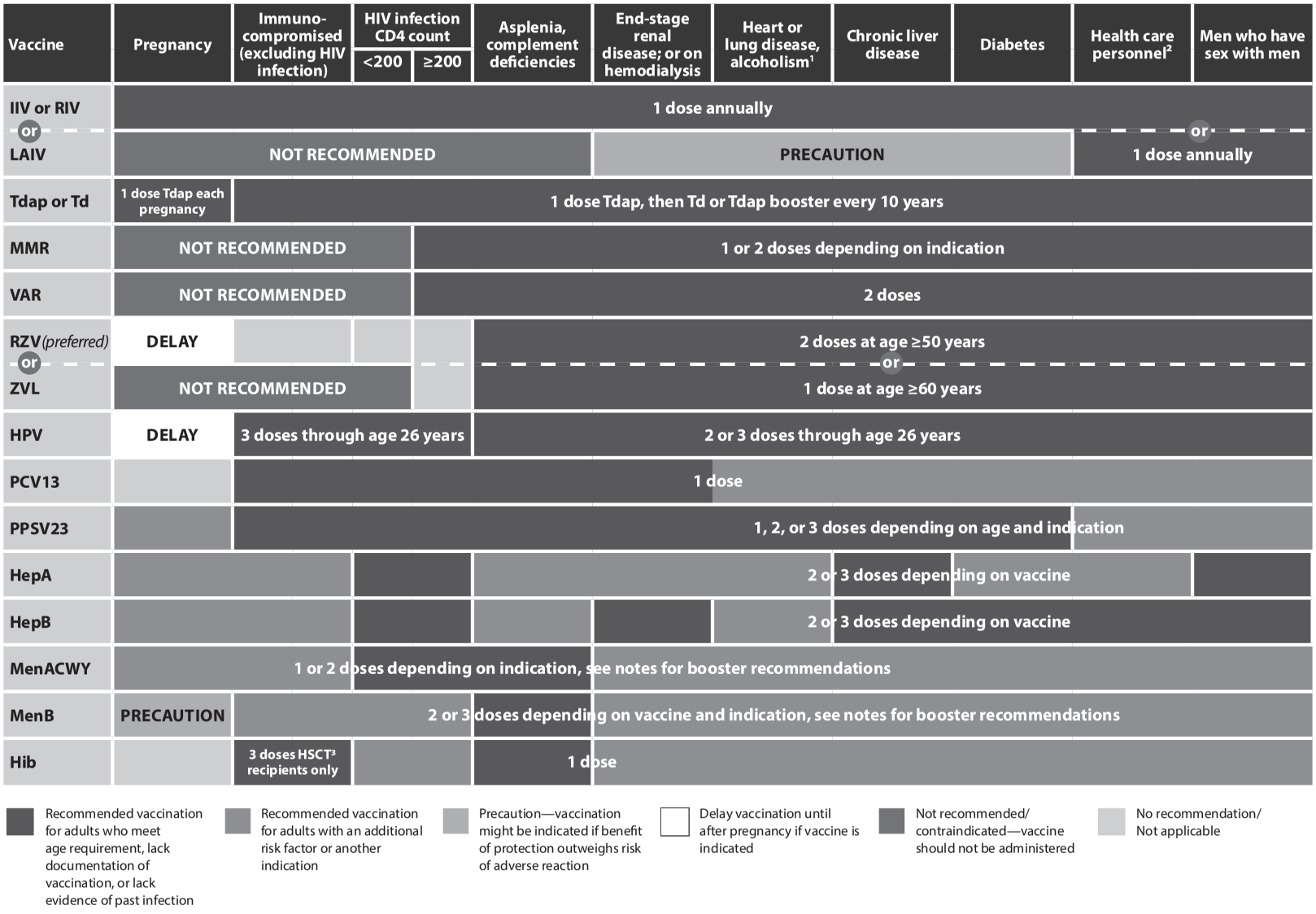

Vaccine
19–26 years
27–49 years
50–64 years
≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV)
or
Influenza live, attenuated (LAIV)
1 dose annually
or
1 dose annually
Tetanus, diphtheria, pertussis (Tdap or Td)
1 dose Tdap, then Td or Tdap booster every 10 years
Measles, mumps, rubella (MMR)
1 or 2 doses depending on indication (if born in 1957 or later)
Varicella (VAR)
2 doses (if born in 1980 or later)
2 doses
Zoster recombinant (RZV) (preferred)
or
Zoster live (ZVL)
2 doses
or
1 dose
Human papillomavirus (HPV)
2 or 3 doses depending on age at initial vaccination or condition
27 through 45 years
Pneumococcal conjugate (PCV13)
1 dose
65 years and older
Pneumococcal polysaccharide (PPSV23)
1 or 2 doses depending on indication
1 dose
Hepatitis A (HepA)
2 or 3 doses depending on vaccine
Hepatitis B (HepB)
2 or 3 doses depending on vaccine
Meningococcal A, C, W, Y (MenACWY)
1 or 2 doses depending on indication, see notes for booster recommendations
Meningococcal B (MenB)
2 or 3 doses depending on vaccine and indication, see notes for booster recommendations
19 through 23 years
Haemophilus influenzae type b (Hib)
1 or 3 doses depending on indication
Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Recommended vaccination based on shared clinical decision-making
No recommendation/ Not applicable

Figure 2. Recommended adult immunization schedule, by vaccine and age group,[a] United States, 2020.

[a]The above recommendations must be read together with the footnotes on the following pages of this schedule.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Adults Aged 19 Years and Older: United States, 2020. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.


Vaccine
Pregnancy
Immuno-compromised (excluding HIV infection)
HIV infection CD4 count
<200
≥200
Asplenia, complement deficiencies
End-stage renal disease; or on hemodialysis
Heart or lung disease, alcoholism[1]
Chronic liver disease
Diabetes
Health care personnel[2]
Men who have sex with men
IIV or RIV
or
LAIV
1 dose annually
or
1 dose annually
NOT RECOMMENDED
PRECAUTION
Tdap or Td
1 dose Tdap each pregnancy
1 dose Tdap, then Td or Tdap booster every 10 years
MMR
NOT RECOMMENDED
1 or 2 doses depending on indication
VAR
NOT RECOMMENDED
2 doses
RZV (preferred)
or
ZVL
DELAY
2 doses at age ≥50 years
or
NOT RECOMMENDED
1 dose at age ≥60 years
HPV
DELAY
3 doses through age 26 years
2 or 3 doses through age 26 years
PCV13
1 dose
PPSV23
1, 2, or 3 doses depending on age and indication
HepA
2 or 3 doses depending on vaccine
HepB
2 or 3 doses depending on vaccine
MenACWY
1 or 2 doses depending on indication, see notes for booster recommendations
MenB
PRECAUTION
2 or 3 doses depending on vaccine and indication, see notes for booster recommendations
Hib
3 doses HSCT[3] recipients only
1 dose
Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended vaccination for adults with an additional risk factor or another indication
Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction
Delay vaccination until after pregnancy if vaccine is indicated
Not recommended/ contraindicated—vaccine should not be administered
No recommendation/ Not applicable

1. Precaution for LAIV does not apply to alcoholism. **2.** See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. **3.** Hematopoietic stem cell transplant.

Figure 3. Vaccines that might be indicated for adults, based on medical and other indications,[a] United States, 2020.

[a]The above recommendations must be read together with the footnotes on the following pages of this schedule.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Adults Aged 19 Years and Older: United States, 2020. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2020

Haemophilus influenzae type b vaccination

Special situations

- **Anatomical or functional asplenia (including sickle cell disease)**: 1 dose if previously did not receive Hib; if elective splenectomy, 1 dose, preferably at least 14 days before splenectomy
- **Hematopoietic stem cell transplant** (HSCT): 3-dose series 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history

Hepatitis A vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis A** (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2/5 months between doses 2 and 3])

Special situations

- **At risk for hepatitis A virus infection**: 2-dose series HepA or 3-dose series HepA-HepB as above
  - **Chronic liver disease** (e.g., persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
  - **HIV infection**
  - **Men who have sex with men**
  - **Injection or noninjection drug use**
  - **Persons experiencing homelessness**
  - **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatitis A virus infection
  - **Travel in countries with high or intermediate endemic hepatitis A**
  - **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)
  - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy
  - **Settings for exposure, including** health care settings targeting services to injection or noninjection drug users or group homes and nonresidential day care facilities for developmentally disabled persons (individual risk factor screening not required)

Hepatitis B vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis B** (identification of risk factor not required): 2- or 3-dose series (2-dose series Heplisav-B at least 4 weeks apart [2-dose series HepB only applies when 2 doses of Heplisav-B are used at least 4 weeks apart] or 3-dose series Engerix-B or Recombivax HB at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2/8 weeks between doses 2 and 3/16 weeks between doses 1 and 3]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2/5 months between doses 2 and 3])

Special situations

- **At risk for hepatitis B virus infection**: 2-dose (Heplisav-B) or 3-dose (Engerix-B, Recombivax HB) series or 3-dose series HepA-HepB (Twinrix) as above
  - **Chronic liver disease** (e.g., persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
  - **HIV infection**
  - **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen [HBsAg]-positive persons; sexually active persons not in mutually monogamous relationships; persons seeking evaluation or treatment for a sexually transmitted infection; men who have sex with men)
  - **Current or recent injection drug use**
  - **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; hemodialysis, peritoneal dialysis, home dialysis, and predialysis patients; persons with diabetes mellitus age younger than 60 years and, at discretion of treating clinician, those age 60 years or older)
  - **Incarcerated persons**
  - **Travel in countries with high or intermediate endemic hepatitis B**
  - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy (Heplisav-B not currently recommended due to lack of safety data in pregnant women)

Human papillomavirus vaccination

Routine vaccination

- **HPV vaccination recommended for all adults through age 26 years**: 2- or 3-dose series depending on age at initial vaccination or condition:
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2, 6 months (minimum intervals: 4 weeks between doses 1 and 2/12 weeks between doses 2 and 3/5 months between doses 1 and 3; repeat dose if administered too soon)
  - **Age 9 through 14 years at initial vaccination and received 1 dose or 2 doses less than 5 months apart**: 1 dose
  - **Age 9 through 14 years at initial vaccination and received 2 doses at least 5 months apart**: HPV vaccination complete, no additional dose needed.
- **If completed valid vaccination series with any HPV vaccine, no additional doses needed**

Shared clinical decision-making

- **Age 27 through 45 years based on shared clinical decision-making**:
  - 2- or 3-dose series as above

Special situations

- **Pregnancy through age 26 years**: HPV vaccination is not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Figure 4. Footnotes from adult immunization schedule, United States, 2020.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Adults Aged 19 Years and Older: United States, 2020. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2020

Influenza vaccination

Routine vaccination

- **Persons age 6 months or older**: 1 dose any influenza vaccine appropriate for age and health status annually
- For additional guidance, see www.cdc.gov/flu/professionals/index.htm

Special situations

- **Egg allergy, hives only**: 1 dose any influenza vaccine appropriate for age and health status annually
- **Egg allergy more severe than hives** (e.g., angioedema, respiratory distress): 1 dose any influenza vaccine appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions
- **LAIV should not be used** in persons with the following conditions or situations:
  - History of severe allergic reaction to any vaccine component (excluding egg) or to a previous dose of any influenza vaccine
  - Immunocompromised due to any cause (including medications and HIV infection)
  - Anatomic or functional asplenia
  - Cochlear implant
  - Cerebrospinal fluid-oropharyngeal communication
  - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment
  - Pregnancy
  - Received influenza antiviral medications within the previous 48 hours
- **History of Guillain-Barré syndrome within 6 weeks of previous dose of influenza vaccine**: Generally should not be vaccinated unless vaccination benefits outweigh risks for those at higher risk for severe complications from influenza

Measles, mumps, and rubella vaccination

Routine vaccination

- **No evidence of immunity to measles, mumps, or rubella**: 1 dose
  - **Evidence of immunity**: Born before 1957 (health care personnel, see below), documentation of receipt of MMR vaccine, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

Special situations

- **Pregnancy with no evidence of immunity to rubella**: MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose
- **Nonpregnant women of childbearing age with no evidence of immunity to rubella**: 1 dose
- **HIV infection with CD4 count ≥200 cells/μL for at least 6 months and no evidence of immunity to measles, mumps, or rubella**: 2-dose series at least 4 weeks apart; MMR contraindicated in HIV infection with CD4 count <200 cells/μL
- **Severe immunocompromising conditions**: MMR contraindicated
- **Students in postsecondary educational institutions, international travelers, and household or close, personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella**: 2-dose series at least 4 weeks apart if previously did not receive any doses of MMR or 1 dose if previously received 1 dose MMR
- **Health care personnel**:
  - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella**: 2-dose series at least 4 weeks apart for measles or mumps or at least 1 dose for rubella
  - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella**: Consider 2-dose series at least 4 weeks apart for measles or mumps or 1 dose for rubella

Meningococcal vaccination

Special situations for MenACWY

- **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use**: 2-dose series MenACWY (Menactra, Menveo) at least 8 weeks apart and revaccinate every 5 years if risk remains
- **Travel in countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis***: 1 dose MenACWY (Menactra, Menveo) and revaccinate every 5 years if risk remains
- **First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) and military recruits**: 1 dose MenACWY (Menactra, Menveo)

Shared clinical decision-making for MenB

- **Adolescents and young adults age 16 through 23 years (age 16 through 18 years preferred) not at increased risk for meningococcal disease**: Based on shared clinical decision-making, 2-dose series MenB-4C at least 1 month apart or 2-dose series MenB-FHbp at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

Special situations for MenB

- **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, microbiologists routinely exposed to *Neisseria meningitidis***: 2-dose primary series MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB booster 1 year after primary series and revaccinate every 2–3 years if risk remains
- **Pregnancy**: Delay MenB until after pregnancy unless at increased risk and vaccination benefits outweigh potential risks

Figure 4. Footnotes from adult immunization schedule, United States, 2020. *(continued)*

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Adults Aged 19 Years and Older: United States, 2020. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Notes Recommended Adult Immunization Schedule, United States, 2020

Pneumococcal vaccination

Routine vaccination

- **Age 65 years or older** (immunocompetent–see www.cdc.gov/mmwr/volumes/68/wr/mm6846a5.htm?s_cid=mm6846a5_w): 1 dose PPSV23
  - If PPSV23 was administered prior to age 65 years, adminster 1 dose PPSV23 at least 5 years after previous dose

Shared clinical decision-making

- **Age 65 years and older** (immunocompetent): 1 dose PCV13 based on **shared clinical decision-making**
  - If both PCV13 and PPSV23 are to be administered, PCV13 should be administered first
  - PCV13 and PPSV23 should be administered at least 1 year apart
  - PCV13 and PPSV23 should not be administered during the same visit

Special situations

(see www.cdc.gov/mmwr/volumes/68/wr/mm6846a5.htm?s_cid=mm6846a5_w)

- **Age 19 through 64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease, diabetes), alcoholism, or cigarette smoking**: 1 dose PPSV23
- **Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorders, HIV infection], chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [e.g., drug or radiation therapy], solid organ transplant, multiple myeloma) or anatomical or functional asplenia (including sickle cell disease and other hemoglobinopathies)**: 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)
- **Age 19 years or older with cerebrospinal fluid leak or cochlear implant**: 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPSV23 at least 5 years after PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)

Tetanus, diphtheria, and pertussis vaccination

Routine vaccination

- **Previously did not receive Tdap at or after age 11 years**: 1 dose Tdap, then Td or Tdap every 10 years

Special situations

- **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis**: At least 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks after Tdap and another dose Td or Tdap 6–12 months after last Td or Tdap (Tdap can be substituted for any Td dose, but preferred as first dose); Td or Tdap every 10 years thereafter
- **Pregnancy**: 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- For information on use of Td or Tdap as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm

Varicella vaccination

Routine vaccination

- **No evidence of immunity to varicella**: 2-dose series 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at least 4 weeks after first dose
  - Evidence of immunity: U.S.-born before 1980 (except for pregnant women and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

Special situations

- **Pregnancy with no evidence of immunity to varicella**: VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility) 1 dose if previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **Health care personnel with no evidence of immunity to varicella**: 1 dose if previously received 1 dose varicella-containing vaccine; 2-dose series 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **HIV infection with CD4 count ≥200 cells/µL with no evidence of immunity**: Vaccination may be considered (2 doses, administered 3 months apart); VAR contraindicated in HIV infection with CD4 count <200 cells/µL
- **Severe immunocompromising conditions**: VAR contraindicated

Zoster vaccination

Routine vaccination

- **Age 50 years or older**: 2-dose series RZV (Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of ZVL (Zostavax) vaccination (administer RZV at least 2 months after ZVL)
- **Age 60 years or older**: 2-dose series RZV 2–6 months apart (minimum interval: 4 weeks; repeat if administered too soon) or 1 dose ZVL if not previously vaccinated. RZV preferred over ZVL (if previously received ZVL, administer RZV at least 2 months after ZVL)

Special situations

- **Pregnancy**: ZVL contraindicated; consider delaying RZV until after pregnancy if RZV is otherwise indicated
- **Severe immunocompromising conditions (including HIV infection with CD4 count <200 cells/µL)**: ZVL contraindicated; recommended use of RZV under review

Figure 4. Footnotes from adult immunization schedule, United States, 2020. *(continued)*

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Adults Aged 19 Years and Older: United States, 2020. Available at www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

A. General Immunization Guidelines
   1. Basic recommendations for adult immunization are based on age and specific vaccines (see Figures 2 and 4).
   2. Certain medical conditions require special consideration when determining whether additional immunizations are recommended (see Figure 3 and footnotes).
   3. On the basis of patient-specific factors, specific vaccines or formulations should be avoided or used with caution.

B. Contraindications and Precautions
   1. Do not administer a vaccine when a contraindication is present due to an increased risk for a serious adverse reaction.
      a. Live vaccines should generally be avoided in patients who are severely immunocompromised.
      b. Pregnant women should not receive live, attenuated vaccines due to theoretical risk to the fetus.
   2. In general, vaccines should be deferred if a precaution is present based on the risk of experiencing a more severe reaction to the vaccine (this risk is less severe than with a contraindication).
      a. A vaccine can be administered when a precaution is present if the benefit outweighs the risks.
      b. All vaccines have a precaution for administration in a patient with a moderate or severe acute illness (with or without fever).
   3. Full lists of contraindications and precautions are available in package inserts or within the Advisory Committee on Immunization Practices (ACIP) Best Practice Guidelines for Immunizations (www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html).

C. Major Changes in the 2020 Adult Immunization Schedule
   1. Figure 2 (known as Table 1 in ACIP document) now combines individuals 19–26 years of age as one column.
   2. Figure 2 (known as Table 1 in ACIP document) now includes an additional color box and footnote to indicate that shared clinical decision-making is recommended for the vaccination (HPV, PCV13, meningococcal).
   3. HPV vaccine is now recommended for all individuals through 26 years of age. Shared clinical decision-making should be considered for individuals 27–45 years of age.
   4. PCV13 should be administered to immunocompetent adults 65 and older after shared decision-making.
   5. Td or Tdap can be used when Td is indicated.
   6. Varicella can be considered for individuals with HIV without evidence of varicella immunity when CD4 counts are 200 cells/mm^3 or greater.

D. Pneumococcal Vaccination
   1. PCV13 is no longer routinely recommended for adults 65 and older. Shared clinical decision-making should be used in those who do not have an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant and who have not received PCV13 previously.
      a. Considerations include: Risk of exposure to PCV13 serotypes (those residing in a nursing home/long-term care facility; those in a setting with low pediatric PCV13 update; those traveling to settings with no pediatric PCV13 program) and risk of pneumococcal disease as a result of underlying medical conditions (chronic heart, lung, or liver disease; diabetes; alcoholism; cigarette use)
      b. If PCV13 is administered to those 65 and older, PPSV23 should be given 1 year later.
   2. All adults 65 and older should receive one dose of PPSV23. If PPSV23 was administered before age 65, administer an additional dose of PPSV23 at least 5 years after the previous dose (and once the patient is 65 or older).

3. Patients should be vaccinated at 19–64 years of age with PPSV23 if they have the following diseases:
   a. Chronic heart disease (heart failure, cardiomyopathies)
   b. Chronic lung disease (COPD, emphysema, asthma)
   c. Chronic liver disease (cirrhosis, alcoholism)
   d. Diabetes
   e. Alcoholism
   f. Cigarette use
   g. No longer recommended for residents in nursing homes or long-term care facilities (as sole indication for administration)
4. Those 19 years and older with immunocompromising conditions should receive: One dose of PCV13, one dose of PPSV23 at least 8 weeks later, one dose of PPSV23 at least 5 years after the previous PPSV23 dose, and one dose of PPSV23 at age 65 or older (at least 5 years after the prior dose)
   a. Congenital or acquired immunodeficiency (lymphocyte deficiencies, HIV infection)
   b. Chronic renal failure
   c. Nephrotic syndrome
   d. Leukemia
   e. Lymphoma
   f. Iatrogenic immunosuppression (drug or radiation therapy)
   g. Solid organ transplantation
   h. Multiple myeloma
   i. Anatomic or functional asplenia
5. Those 19 years and older with a cerebrospinal fluid leak or cochlear implant should receive: One dose of PCV13, one dose of PPSV23 at least 8 weeks later, and one dose of PPSV23 at age 65 or older (at least 5 years after previous dose)

E. Influenza Vaccination
   1. Egg allergy
      a. If an adult has an egg allergy of any severity, recombinant influenza vaccine (RIV), which is free of egg protein, can be administered.
      b. If an adult has experienced only hives after eating eggs or egg-containing foods, he or she can safely receive inactivated influenza vaccine (IIV) with additional safety measures. Avoid live-attenuated influenza vaccine nasal spray.
      c. Some people who report egg allergies may not actually be allergic to eggs. Those who can eat a lightly cooked egg (e.g., scrambled egg) without a reaction are likely not allergic and can safely receive any influenza vaccine.
   2. Live-attenuated influenza vaccine in adults
      a. Nasal mist
      b. Indicated for those 49 years and younger, except for those:
         i. Who are immunocompromised as the result of any cause (including medications and HIV infection)
         ii. With anatomic or functional asplenia
         iii. With a cochlear implant
         iv. With a cerebrospinal fluid-oropharyngeal communication condition
         v. Close contacts or caregivers of severely immunosuppressed individuals who require a protected environment
         vi. Pregnancy
         vii. Received influenza antiviral medications in the past 48 hours

3. If patients have a history of Guillain-Barré syndrome within 6 weeks of a previous dose of influenza vaccine, they should generally not be vaccinated.
4. Influenza vaccination in SARS-CoV-2 infection (COVID-19)
    a. Clinical experience is limited with influenza vaccination in patients who have suspected or confirmed COVID-19. Postponing vaccination should be considered until the patient has recovered from the acute illness.

F. Herpes Zoster Vaccine
1. Shingrix
    a. Preferred herpes zoster vaccine product
    b. Zoster vaccine, recombinant
    c. Two-dose regimen at 0 and 2–6 months
    d. Efficacy close to 90% compared with placebo
    e. Storage and reconstitution differ from Zostavax
        i. Stored in refrigerator
        ii. Used within 6 hours of reconstitution

G. HPV Vaccine
1. Nine-valent HPV vaccine (9vHPV) is available and may be used for routine HPV vaccination of both females and males.
2. HPV vaccine recently had expanded ages approved for use. It is now approved to be used in males and females 9-45 years of age. HPV vaccination is now recommended as a catch-up vaccine for all people through age 26. For adults 27–45 years of age, shared decision-making is recommended because of lack of widespread public health benefit but recognition that some people may benefit
3. The series is two doses when started before age 15, with at least 5 months between the two doses. If the series is started after age 15 or the doses are separated by less than 5 months, the three-dose series (at 0, 1–2, and 6 months) is still recommended.
4. Revaccination with 9vHPV is not recommended if the complete regimen of 2vHPV or 4vHPV has previously been received. The 9vHPV regimen may be completed if started with the 2vHPV or 4vHPV product.

Patient Cases

10. A 71-year-old woman with COPD is taking tiotropium (Spiriva) inhaled 1 capsule/day. She received the influenza vaccine last October, her last Td vaccine was at age 65, and her PPSV23 was given at age 60. She has not yet received the zoster vaccine, but she had an episode of severe zoster infection 5 years ago. Which is the most appropriate choice of vaccines for the patient's October internal medicine clinic appointment?
    A. Only the influenza vaccine.
    B. Influenza and PCV13 vaccines.
    C. Influenza, PCV13, and RZV.
    D. Influenza, PCV13, RZV, and Tdap.

11. A 20-year-old woman who is going away to college presents for a physical examination in July. She will be living in the dormitory. She smokes 1/2 pack/day but has no other medical conditions. She is up to date on all of her routine childhood vaccines until the age of 9 but has not received any vaccines in the past 11 years. She is not sexually active. Which is the most appropriate choice of vaccines to be given today?
    A. Td and HPV.
    B. Tdap, MenACWY, and HPV.
    C. MenACWY, PPSV23, and Td.
    D. MenACWY, PPSV23, Tdap, and HPV.

12. A 21-year-old man with type 1 diabetes presents for an influenza vaccine. He has an egg allergy, with angioedema and difficulty breathing after eating eggs. Which is the most appropriate influenza vaccination plan for this patient?
    A. IIV, RIV, or live-attenuated influenza vaccine may be used; observe patient for 30 minutes.
    B. Either IIV or RIV may be used; observe patient for 30 minutes.
    C. Only RIV should be used.
    D. He should not receive any type of influenza vaccine.

REFERENCES

Asthma

1. Agency for Healthcare Research and Quality (AHRQ). Improving the Quality of Asthma Care. Available at https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/asthmaqual/index.html. Accessed August 23, 2020.
2. FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called long-acting beta-agonists (LABAs). June 2, 2010. Available at http://wayback.archive-it.org/7993/20170112031853/http:/www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm. Accessed August 23, 2020.
3. FDA Drug Safety Communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). December 20, 2017. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-no-significant-increase-risk-serious-asthma-outcomes. Accessed August 23, 2020.
4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2020. Available at www.ginasthma.org. Accessed August 23, 2020.
5. Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015 Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). Available at www.goldcopd.org. Accessed August 23, 2020.
6. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomized, double-blind, placebo-controlled trial. Lancet 2011;377:650-7.
7. National Institutes of Health National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program (NAEPP) guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. July 2007. Available at https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed August 23, 2020.
8. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial (SMART): a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.
9. Perera BJ. Salmeterol Multicentre Asthma Research Trial (SMART): interim analysis shows increased risk of asthma-related deaths. Ceylon Med J 2003;48:99.
10. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma (TALC study). N Engl J Med 2010;363:1715-26.
11. Price D, Musgrave SD, Shepstone L, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. N Engl J Med 2011; 364:1695-707.

Chronic Obstructive Pulmonary Disease

1. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.
2. Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ 2010;341:c5462.
3. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581-6.
4. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease (the TORCH study). N Engl J Med 2007;356:775-89.
5. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012;9:CD009157.
6. Criner CJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD. American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest 2015; 147:894-942.

7. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. N Engl J Med 2014; 370:2201-10.
8. Ernst P, Gonzalez AP, Brassard P, et al. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. Am J Respir Crit Care Med 2007;176:162-6.
9. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, 2008. Available at https://www.ncbi.nlm.nih.gov/books/NBK63952/. Accessed August 23, 2020.
10. Global Initiative for Chronic Obstructive Lung Disease Workshop Executive Summary: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2020 Update. Available at www.goldcopd.org. Accessed August 23, 2020.
11. Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015 Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). Available at www.goldcopd.org. Accessed August 23, 2020.
12. Heffner JE, Mularski RA, Calverley PM. COPD performance measures: missing opportunities for improving care. Chest 2010;137:1181-9.
13. Ingebrigtsen TS, Marott JL,Nordestgaard BG, et al. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. Thorax 2015;70:33-40.
14. Lahousee L, Loth DW, Joos GF, et al. Statins, systemic inflammation and risk of death in COPD: the Rotterdam study. Pulm Pharmacol Ther 2013; 26:212-7.
15. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA 2013;309:2223-31.
16. Lowry KP, Gazelle GS, Gilmore ME, et al. Personalizing annual lung cancer screening for patients with chronic obstructive pulmonary disease: a decision analysis. Cancer 2015;121:1556-62.
17. Lu Y, Chang R, Yao J, et al. Effectiveness of long-term using statins in COPD - a network meta-analysis. Respir Res 2019;20:Article 17.
18. McEvoy CE, Neiwoehner DE. Adverse effects of corticosteroid therapy for COPD: a critical review. Chest 1997;111:732-43.
19. Nannini LJ, Cates CJ, Lasserson TJ, et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2007;4:CD003794.
20. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011;155:179-91.
21. Rutten FH, Zuithoff NP, Hak E, et al. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med 2010;170:880-7.
22. Salpeter SR, Ormiston T, Salpeter E, et al. Cardioselective beta-blockers for chronic obstructive pulmonary disease [review]. Cochrane Database Syst Rev 2002;2:CD003566. Update in: Cochrane Database Syst Rev 2005;4:CD003566.
23. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease. Arch Intern Med 2009;169:219-29.
24. Stoller JK. Alpha-1 antitrypsin deficiency: an underrecognized, treatable cause of COPD. Cleve Clin J Med 2016;83:507-14.
25. Uzun S, Djamin RS, Kluytmans JA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014;2:361-8.
26. VanDerMolen T, Willemse BW, Schokker S, et al. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes 2003;1:13.
27. van Grunsven PM, van Schayck CP, Dereene JP, et al. Long-term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. Thorax 1999;54:7-14.

28. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD (POET-COPD study). N Engl J Med 2011;364:1093-103.
29. Wang MT, Lo YW, Tsai CL, et al. Statin use and risk of COPD exacerbation requiring hospitalization. Am J Med 2013;126:598-606.
30. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med 2016;374: 2222-34.
31. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:741-50.
32. Young RP, Hopkins RJ, Chan W, et al. Effect of statin therapy on mortality in COPD: analysis of cause specific deaths in a national cohort study. Am J Respir Crit Care Med 2013;187:A6017.

Immunizations

1. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Adults Aged 19 Years and Older: United States, 2020. Available at www.cdc.gov/vaccines/schedules hcp/imz/adult.html. Accessed August 23, 2020.
2. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices – United States, 2020-21 influenza season. MMWR Recomm Rep 2020;69:1-24.
3. Kroger AT, Duchin J, Vazquez M. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Available at https:// www.cdc.gov/vaccines/hcp/acip-recs/general-recs/ index.html. Accessed August 23, 2020.
4. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:1069-75. Available at https:// www.cdc.gov/mmwr/volumes/68/wr/mm6846a5. htm?s_cid=mm6846a5_w. Accessed August 23, 2020.
5. Meites E, Szilagyi PG, Chesson HW, et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:698-702. Available at https:// www.cdc.gov/mmwr/volumes/68/wr/mm6832a3. htm. Accessed August 23, 2020.
6. Shingrix [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline, October 2019.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Her symptom frequency of twice weekly, her FEV_1 of more than 80% of predicted (normal), and the lack of interference with activity are consistent with intermittent asthma. Answer A is incorrect; her night awakenings for asthma symptoms occur three times per month, which is consistent with mild persistent asthma. Therefore, Answer B is correct. The specific level of persistent asthma is based on the most severe category met. Answers C and D are incorrect because only one of her signs and symptoms falls under mild persistent asthma (nighttime awakenings), and the rest fall under intermittent asthma.

2. Answer: A

Because she has mild persistent asthma, step 2 is recommended for initial treatment. Answer A is correct given that step 2 treatment involves adding a low-dose ICS daily or an as-needed low-dose ICS-formoterol. Answer B is incorrect because montelukast is an alternative therapy (not first line) for step 2. Answer C is incorrect; mometasone 220 mcg 2 puffs once daily is a medium-dose ICS (alternative step 3). Budesonide/formoterol at the dose listed is a low-dose ICS plus a LABA (step 3 therapy), making Answer D incorrect.

3. Answer: B

Her asthma is classified as not well controlled because of the frequency of her daytime symptoms and her need to use albuterol more than 2 days/week. When asthma is classified as not well controlled, the recommendation is to increase to the next step of treatment. The patient would now be classified as needing step 3 treatment. The recommended treatment for step 3 is a low-dose ICS plus a LABA. Answer A is incorrect because the recommended treatment for step 3 is a daily low-dose ICS plus a LABA. Answer B is correct because the fluticasone propionate/salmeterol DPI is a low-dose ICS plus a LABA (a step 3 treatment). Adding montelukast is an alternative therapy for step 2 and would not be the preferred option, making Answer C incorrect. Answer D is incorrect; mometasone 220 mcg/puff 2 puffs daily is a medium-dose ICS.

4. Answer: B

Given the patient's twice-weekly nighttime symptoms, he has moderate persistent asthma and needs step 3 therapy. A medium-dose ICS alone or a low-dose ICS plus a LABA is preferred as initial therapy in this age group (6–11 years). Answer A is incorrect because fluticasone 44 mcg 1 puff twice daily is a low-dose ICS for this age group. Answer B is correct; fluticasone 110 mcg/puff is a medium-dose ICS. Fluticasone/salmeterol 100/50 twice daily is a medium-dose ICS plus a LABA, which is step 4 in this age group; therefore, Answer C is incorrect. Answer D is incorrect because montelukast is not recommended as monotherapy for moderate persistent asthma in this age group; montelukast is recommended only in combination with a low-dose ICS.

5. Answer: C

Because the patient is experiencing shortness of breath at rest, has trouble with conversation, and has an FEV_1 less than 50% of expected, his asthma exacerbation is classified as severe. For severe asthma exacerbations in the ED setting, pharmacologic treatment is recommended in addition to oxygen to achieve an Sao_2 of 93%–98%; therefore, Answer A is incorrect. Answer B is incorrect because a high-dose inhaled SABA should be combined with ipratropium and administered by either a nebulizer or an MDI with valved holding chamber every 20 minutes for 1 hour or continuously for severe asthma exacerbations in the ED setting. Answer C is correct because it correctly combines a SABA with ipratropium and includes OCSs. Answer D correctly provides a SABA with ipratropium; however, intravenous corticosteroids are not recommended unless the patient has an incomplete response to inhaled and oral treatments.

6. Answer: B

Answer A is incorrect because the patient's FEV_1 is less than 80% of predicted, and his mMRC score is greater than 1. Answer B is correct in light of his post-bronchodilator FEV_1 of 50%–80%, history of 1 exacerbation that did not lead to hospitalization in the past year, and mMRC score of 2 or more. Answer C is incorrect; the patient has an FEV_1 of 50%–80%, has had only 1 exacerbation that did not lead to hospitalization, and has an mMRC score greater than 1. Answer D is incorrect because the patient has an FEV_1 of 50%–80%

and has only had 1 exacerbation that did not lead to hospitalization.

7. Answer: B

Answer A is incorrect; according to the GOLD guidelines, the recommended treatment for patient group B is regular treatment with an LA bronchodilator (either a LABA or LAMA) in addition to a SA bronchodilator as needed. Answer B is correct; salmeterol is a LABA. Answer C is incorrect because the LAMA and LABA combination is recommended as treatment intensification for groups B and C or initial treatment for group D. Answer D is incorrect because ICSs are recommended only as part of treatment intensification for group D; roflumilast is recommended only if the FEV_1 is less than 50% of predicted with chronic bronchitis, and the patient has a history of frequent exacerbations.

8. Answer: A

This patient is in GOLD risk group B, according to her FEV_1, CAT score, and lack of exacerbations. She is receiving the first-line therapy with a LAMA (tiotropium). Because her control is worsening, her treatment should be intensified, for which combined LA bronchodilators are recommended (LABA plus LAMA). Salmeterol is a LABA; therefore, Answer A is correct. Answer B is incorrect because the long-term use of antibiotics is currently recommended only in group D patients who are former smokers with an eosinophil count < 100 cells/mcL that require treatment intensification. Answers C and D both contain the option of adding fluticasone in some form. Inhaled corticosteroids are recommended only as an alternative treatment intensification regimen in group C when eosinophils are > 300 cells/mcL and for patients in Group D (initial treatment with LABA when eosinophils > 300 cells/mcL or as add-on to LABA/LAMA as treatment intensification when eosinophils > 100 cells/mcL); therefore, Answers C and D are incorrect.

9. Answer: D

Answer A is incorrect because the patient's symptoms indicate that she has a COPD exacerbation and additional treatment is warranted. According to the latest GOLD guidelines, OCSs are indicated in most exacerbations. The recommended dose is oral prednisone 40 mg daily for 5 days. Antibiotic treatment is also indicated because the patient has all three cardinal symptoms of airway infection: increased sputum purulence, increased sputum volume, and increased dyspnea. Azithromycin is one of the recommended antibiotics. Although Answers B and C contain components of the correct treatment for this patient's COPD exacerbation, neither Answer B nor Answer C is complete. Answer D is correct because it incorporates both an OCS and an antibiotic for this patient's COPD exacerbation.

10. Answer: D

The CDC recommends that the influenza vaccine be given every year to every person 6 months and older. Adults 65 and older should engage in shared clinical decision-making regarding the use of PCV13. This patient is likely to benefit from administration of PCV13, given her history of chronic lung disease (COPD). Because it has been more than 5 years since her previous PPSV23 vaccination, she should receive the PCV13 vaccination at the October visit and a second PPSV23 vaccination at least 1 year after the PCV13 administration. Recombinant zoster vaccination is recommended in all adults 50 and older, regardless of previous zoster infection. The Tdap vaccine is recommended as a one-time replacement for Td in all people, now including those 65 and older. Answer A is incorrect because it does not address the need for PCV13, zoster vaccine, or Tdap. Answer B is incorrect because it does not address zoster or Tdap vaccination. Answer C is incorrect because it does not include Tdap. Answer D is correct because it includes all four of the appropriate vaccinations for October's visit.

11. Answer: D

First-year college students up to age 21 who live in dormitories, if not previously vaccinated on or after age 16, should receive the meningococcal vaccine (MenACWY; Menactra, Menveo). The PPSV23 is recommended for smokers 19–64 years of age, and this patient is a smoker. The Td vaccine should be given every 10 years. In adults younger than 65, a one-time dose of Tdap should be given, regardless of the time interval since the most recent tetanus vaccination. The HPV vaccine is recommended for all people 9–26 years of age. Ideally, it should be given before the start of sexual activity, but it should still be administered to sexually active individuals. Answer A is incorrect because it does not include a meningococcal or pneumococcal vaccine and recommends Td instead of Tdap. Answer B is incorrect because it does not include the

pneumococcal vaccine. Answer C is incorrect because it does not include HPV vaccine and recommends Td instead of Tdap. Answer D appropriately includes all four necessary immunizations for the patient's visit today and is correct.

12. Answer: C

Answer A is incorrect because of this patient's history of severe allergy to eggs, as indicated by angioedema. Inactivated influenza vaccine is an option in patients who have had mild allergic reactions to eggs but should not be used in the setting of a severe allergy. Answer B is incorrect and Answer C is correct because in people with a severe egg allergy, only RIV can be used. Answer D is incorrect because the patient is still eligible for an influenza vaccine as long as it is RIV.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

Answer A is incorrect because patients with mild intermittent have symptoms 2 days or fewer per week. This patient uses the inhaler throughout the day every day and sometimes at night, indicating that she has daily symptoms. Answer B is incorrect because the patient is having daily symptoms, and patients with mild persistent asthma have symptoms more often than 2 days per week but fewer than daily. Answer C is correct because the patient is having daily symptoms. Answer D is incorrect because "severe persistent" means that the frequency of symptoms is throughout the day, nighttime symptoms often occur seven times a week, a SABA is needed several times a day, normal activity is extremely limited, the FEV_1 is less than 60% of predicted, and the FEV_1/FVC is reduced by more than 5%.

2. Answer: C

Moderate asthma requires step 3 treatment for control. Step 3 preferred treatment is an inhaled steroid (low dose) plus a LABA. Answer A is incorrect because low-dose fluticasone is considered step 2 treatment. Answer B is incorrect because montelukast is an alternative treatment for step 2. Answer C is correct; fluticasone low dose plus salmeterol is the preferred step 3 treatment. Answer D is incorrect because high-dose fluticasone monotherapy is not recommended for treatment of any step of asthma treatment.

3. Answer: D

Answer A is incorrect because nominal data contain no quantitative value and are simply labels. Ordinal data is a measure of non-numeric concepts in which the order of the value is important but the differences between values are not truly known, making Answer B incorrect. Answer C is incorrect because although interval data are ranked in a specific order with a consistent level of magnitude difference between units, there is no absolute zero. Answer D is correct because ratio data are ranked in a specific order with a consistent level of magnitude difference between units, with an absolute zero.

4. Answer: B

The percentage of patients receiving fluticasone/salmeterol who have an asthma-related hospitalization will be compared with the percentage of patients receiving fluticasone who have an asthma-related hospitalization. We assume that these two groups are normally distributed. These data are considered nominal. Use of ANOVA is appropriate when there are more than two treatment groups; therefore, Answer A is incorrect. Answer B is correct because the chi-square test is appropriate for analyzing nominal or categorical data. The Mann-Whitney *U* test is appropriate when continuous data are not normally distributed; therefore, Answer C is incorrect. Answer D is incorrect because the Student unpaired t-test is used for continuous data that are normally distributed.

5. Answer: B

Answer A is incorrect because the influenza vaccine is recommended in people with chronic cardiovascular or pulmonary diseases such as asthma. However, usually the influenza vaccine is given in the fall or early winter to offer protection when the risk of infection is highest. Answer B is correct; the pneumococcal vaccine is recommended in people 19–64 years of age with asthma, and this patient falls into this category. Answer C is incorrect because the tetanus booster (Td) is recommended every 10 years, and it has not been 10 years since this patient's last Td, which was given as Tdap. The herpes zoster vaccine is recommended by the CDC for adults 50 and older so Answer D is incorrect.

6. Answer: B

This patient is in GOLD 2, group B. A single LA bronchodilator is the first choice of medication treatment. Answer A is incorrect because an ICS is recommended only in patient groups C and D and should never be used as monotherapy in COPD. Tiotropium is a LA bronchodilator (anticholinergic) that would be appropriate in this patient, making Answer B correct. (A LABA would also be appropriate, but it was not one of the choices.) Answer C is incorrect because the ICS/LABA combination is only a recommended alternative for treatment intensification if a patient is in group C or D. Answer D is incorrect because roflumilast is only indicated in severe COPD (FEV_1 less than 50% of predicted) associated with chronic bronchitis when the patient has a history of frequent exacerbations.

7. Answer: A

Answer A is correct because dyspnea that is progressive, persistent, and worse with exertion is a hallmark symptom of COPD. Answer B is incorrect because spirometry findings of an FEV_1/FVC less than 70% of predicted are required for a diagnosis of COPD. Answer C is incorrect because although a chronic cough is usually a symptom of COPD, this cough is rarely only nocturnal and is most often present throughout the day. The CAT has a score range of 5–30, with higher scores indicating worse COPD. A CAT score of 5 is within the upper limit of normal scores, making Answer D incorrect.

8. Answer: C

To correctly identify the patient group, the FEV_1, exacerbation history, and current symptoms must be assessed. An exacerbation leading to a hospitalization places him at high risk of recurrent exacerbations; and an mMRC score of 1 indicates that he currently has few symptoms. On the basis of this information combined, the patient would be in GOLD 2, group C, making Answers A, B, and D incorrect. Answer C is correct because it appropriately places the patient in group C, with the correct initial treatment for a patient in group C being a LA anticholinergic such as tiotropium.

9. Answer: D

During each pregnancy, it is recommended that the woman receive a Tdap vaccination, regardless of the time since her last Td or Tdap immunization. Therefore, Answers A and B are incorrect because they do not include Tdap. Answer C is incorrect because an annual influenza vaccine is recommended for all pregnant women, and the visit is taking place in October, when it would be appropriate to administer the influenza vaccine. Answer D is correct because it includes both Tdap and influenza.

10. Answer: A

It is recommended that a one-time dose of Tdap be substituted for Td in all patients and that the HPV vaccine be administered to males up to age 45. Therefore, Answer A is correct. Answer B is incorrect because it is inappropriate to administer the influenza vaccine in July, and the patient has no risk factors indicating that he would benefit from the meningococcal vaccine (e.g., he is not living in a college dormitory and does not travel frequently). Answer C is incorrect because the patient should receive Tdap in place of the Td booster and does not need the meningococcal vaccine. Answer D is incorrect because the patient should receive Tdap in place of the Td booster, and it is not appropriate to administer the influenza vaccine in July.